A.M.A. Archives OF

INTERNAL MEDICINE

STUDIES IN IRON TRANSPORTATION AND METABOLISM
RUTH STEINKAMP, M.D., ET AL.

PARAHEMOPHILIA
CHARLES A. OWEN Jr., M.D., ET AL.

CHLORPROMAZINE AS A THERAPEUTIC AGENT IN CLINICAL MEDICINE
JOHN H. MOYER, M.D., ET AL.

USE OF PLANIGRAPHY IN DEMONSTRATION OF CALCIFICATION OF HEART VALVES AND ITS SIGNIFICANCE
LOUIS A. SOLOFF, M.D., ET AL.

STUDIES ON URINARY LIPASE
MARTIN M. NOTHMAN, M.D., ET AL.

ASCHOFF BODIES IN LEFT AURICULAR APPENDAGES OF PATIENTS WITH MITRAL STENOSIS
BENJAMIN MANCHESTER, M.D., ET AL.

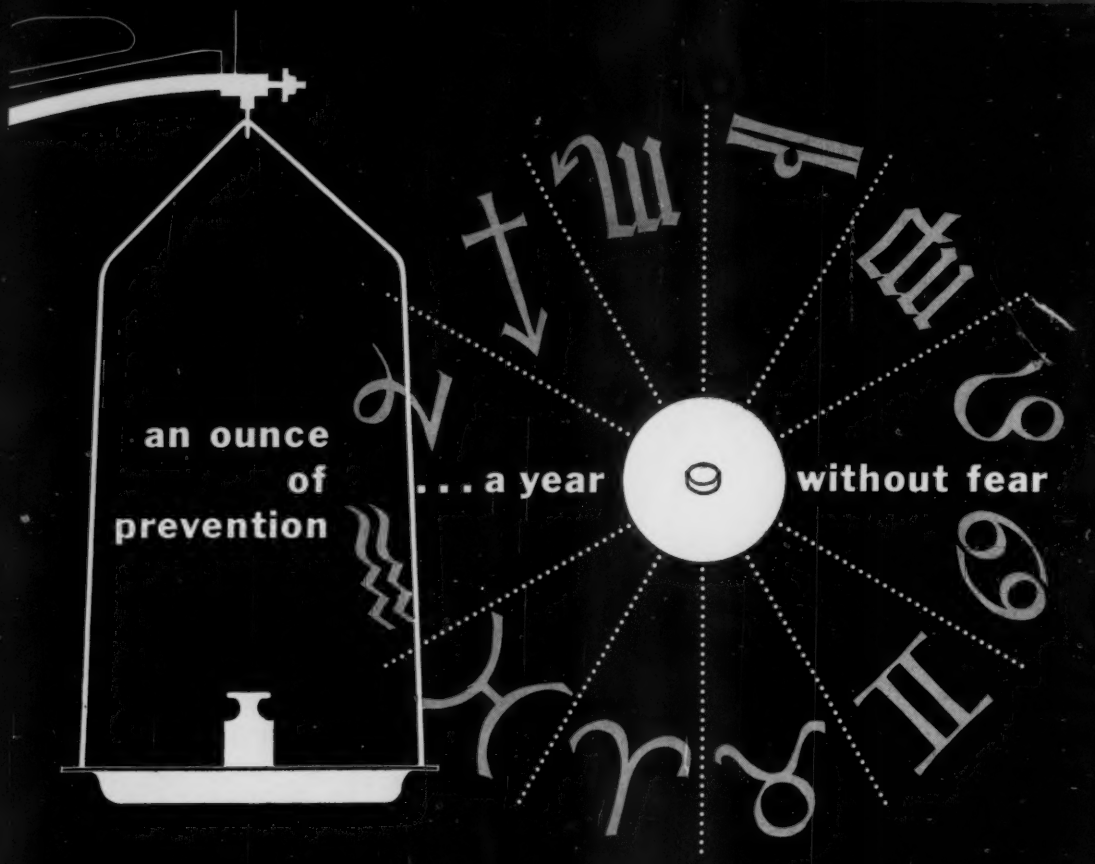
CARBOHYDRATE METABOLISM IN BRAIN DISEASE
DOROTHY H. HENNEMAN, M.D., ET AL.

MANAGEMENT OF CHRONIC NEPHRITIS
GUY W. DAUGHERTY, M.D.

COMPLETE CONTENTS ON FIRST PAGE

FEBRUARY 1955
VOLUME 95 NUMBER 2

AMERICAN MEDICAL ASSOCIATION Publication



for the patient with angina pectoris

With Peritrate, a long-acting coronary vasodilator, an ounce of prevention (28,350 mg. of Peritrate) lasts a full year or longer, since only 10 or 20 mg. are needed to protect most patients for 4 to 5 hours. Yet, no arithmetic formula can adequately define the effectiveness of Peritrate in providing dramatic relief from pain and from the fear of anginal attacks.

According to tests made by Russek and coworkers, Peritrate is unexcelled in exerting a prolonged prophylactic effect in angina pectoris. The results achieved ". . . were comparable to those obtained with glyceryl trinitrate (nitroglycerin), but the duration of action was considerably more prolonged."[1] Patients on Peritrate generally exhibit significant EKG improvement,[1,2] and their need for nitroglycerin is often reduced.[3] A continuing year-round schedule of 10 or 20 mg. 4 times a day will usually:

1. reduce the number of attacks (in 8 out of 10 patients[2,3]);
2. reduce the severity of attacks not prevented.

Available in both 10 mg. and 20 mg. tablets and, for extended night-long protection, in Enteric Coated tablets (10 mg.).

1. Russek, H. I.; Urbach, K. F.; Doerner, A. A., and Zohman, B. L.: J.A.M.A. *153*:207 (Sept. 19) 1953. 2. Winsor, T., and Humphreys, P.: Angiology *3*:1 (Feb.) 1952. 3. Plotz, M.: New York State J. Med. *52*:2012 (Aug. 15) 1952.

Peritrate®

tetranitrate

(BRAND OF PENTAERYTHRITOL TETRANITRATE)

WARNER-CHILCOTT

TABLE OF CONTENTS

VOLUME 95 FEBRUARY 1955 NUMBER 2

ORIGINAL ARTICLES

PAGE

Studies in Iron Transportation and Metabolism 181
Ruth Steinkamp, M.D.; Reubenia Dubach, Ph.D., and Carl V. Moore, M.D., St. Louis

Parahemophilia 194
Charles A. Owen Jr., M.D., and Talbert Cooper, M.D., Rochester, Minn.

Chlorpromazine as a Therapeutic Agent in Clinical Medicine 202
John H. Moyer, M.D.; Vernon Kinross-Wright, M.D., and R. Milton Finney, M.D., Houston, Texas

Use of Planigraphy in Demonstration of Calcification of Heart Valves and Its Significance 219
Louis A. Soloff, M.D.; Jacob Zatuchni, M.D., and Herbert Fisher, M.D., Philadelphia

Studies on Urinary Lipase 224
Martin M. Nothman, M.D.; Joseph H. Pratt, M.D., and Allan D. Callow, M.D., Boston

Aschoff Bodies in Left Auricular Appendages of Patients with Mitral Stenosis 231
Benjamin Manchester, M.D., Washington, D. C.; Thomas M. Scotti, M.D., Coral Gables, Fla.; Mardelle L. Reynolds, A.B., and Wilhelmina H. Dawson, Washington, D. C.

Carbohydrate Metabolism in Brain Disease 241
Dorothy H. Henneman, M.D., Boston; Mark D. Altschule, M.D., and Rose-Marie Goncz, Waverley, Mass.

TREATMENT IN INTERNAL MEDICINE

Management of Chronic Nephritis 247
Guy W. Daugherty, M.D., Rochester, Minn.

PROGRESS IN INTERNAL MEDICINE

Syphilis 256
Herman Beerman, M.D.; Ira L. Schamberg, M.D.; Leslie Nicholas, M.D., Philadelphia, and Lawrence Katzenstein, M.D., Wilmington, Del., with the collaboration of T. Guthe, M.D., and C. J. Hackett, M.D., Geneva, Switzerland

CASE REPORTS

Fatal Staphylococcal Endocarditis Treated with Erythromycin 320
Robert J. Roantree, M.D., and Lowell A. Rantz, M.D., San Francisco

Autoimmune Hemolytic Disease in Acute Leukemia 326
Abraham M. Frumin, M.D., and Albert Kohn, B.S., Philadelphia

Significant Case of Pneumoconiosis in a Soft-Coal Worker 328
Louis L. Friedman, M.D., Birmingham, Ala.

Felty's Syndrome 333
Thomas J. Fitzpatrick, M.D., and Lewis W. Woodruff, M.D., Joliet, Ill.

Periodic Disease 337
Edmund Shwayri, M.D., and Nevin Tutunji, M.D., Beirut, Lebanon

Ostial Stenosis of Coronary Arteries in Nine-Year-Old Girl 341
N. Goormaghtigh, M.D.; L. De Vos, M.D., and A. Blancquaert, M.D., Ghent, Belgium

Treatment of Hemochromatosis by Massive Venesection 349
Ralph M. Myerson, M.D., Philadelphia, and Irvin N. Carroll, M.D., Wilmington, Del.

REGULAR DEPARTMENTS

Correspondence 354

News and Comment 193, 325, and 356

SCIENTIFIC EXHIBITS

Endocrine Therapy of Metastatic Breast Cancer 357
Olof H. Pearson, M.D.; Charles D. West, M.D.; Min Chiu Li, M.D.; John P. Maclean, M.D., and Norman Treves, M.D., New York

A. M. A.
ARCHIVES OF INTERNAL MEDICINE

VOLUME 95 FEBRUARY 1955 NUMBER 2

COPYRIGHT, 1955, BY THE AMERICAN MEDICAL ASSOCIATION

EDITORIAL BOARD

PAUL S. RHOADS, Chief Editor, Chicago

WILLIAM B. BEAN, Iowa City
ARTHUR BLOOMFIELD, San Francisco
GEORGE E. BURCH, New Orleans
HUGH R. BUTT, Rochester, Minn.
CHARLES S. DAVIDSON, Boston
LOUIS LEITER, New York

BRUCE K. WISEMAN, Columbus, Ohio

AUSTIN SMITH, Editor, A. M. A. Scientific Publications
GILBERT S. COOPER, Managing Editor, Specialty Journals

AMERICAN MEDICAL ASSOCIATION
Scientific Publications

The Journal of the American Medical Association. Weekly. Annual Subscription Price, $15.00.

Quarterly Cumulative Index Medicus. Issued Twice a Year. Subscription Price, Calendar year, $20.00.

A. M. A. Specialty Journals
Monthly

A. M. A. Archives of Internal Medicine. Paul S. Rhoads, M.D., Chief Editor, American Medical Association, 535 N. Dearborn St., Chicago 10. Price, $10.00; Canada, $10.50; Foreign, $11.50; individual copy, $1.00.

A. M. A. Archives of Dermatology. Paul A. O'Leary, M.D., Chief Editor, 200 First St. S.W., Rochester, Minn. Price, $12.00; Canada, $12.50; Foreign, $13.50; individual copy, $1.25.

A. M. A. Archives of Ophthalmology. Francis Heed Adler, M.D., Chief Editor, 313 S. 17th St., Philadelphia 5. Price, $12.00; Canada, $12.50; Foreign, $13.50; individual copy, $1.25.

A. M. A. Archives of Surgery. Waltman Walters, M.D., Chief Editor, American Medical Association, 535 N. Dearborn St., Chicago 10. Price, $14.00; Canada, $14.50; Foreign, $15.50; individual copy, $1.25.

A. M. A. American Journal of Diseases of Children. Clifford G. Grulee, M.D., Chief Editor, 610 Church St., Evanston, Ill. Price, $12.00; Canada, $12.50; Foreign, $13.50; individual copy, $1.25.

A. M. A. Archives of Pathology. Paul R. Cannon, M.D., Chief Editor, Department of Pathology, University of Chicago, The School of Medicine, 950 E. 59th St., Chicago 37. Price, $8.00; Canada, $8.50; Foreign, $9.25; individual copy, $1.00.

A. M. A. Archives of Neurology and Psychiatry. Tracy J. Putnam, M.D., Chief Editor, 450 N. Bedford Drive, Beverly Hills, Calif. Price, $12.00; Canada, $12.50; Foreign, $13.50; individual copy, $1.25.

A. M. A. Archives of Otolaryngology. George M. Coates, M.D., Chief Editor, 1721 Pine St., Philadelphia 3. Price, $12.00; Canada, $12.50; Foreign, $13.50; individual copy, $1.25.

A. M. A. Archives of Industrial Health. Prof. Philip Drinker, Chief Editor, Dept. of Industrial Hygiene, Harvard University School of Public Health, 55 Shattuck St., Boston 15. Price, $8.00; Canada, $8.50; Foreign, $9.00; individual copy, $1.00.

Checks, money orders, and drafts should be made payable to the American Medical Association, 535 North Dearborn Street, Chicago 10.

Published Monthly by

AMERICAN MEDICAL ASSOCIATION

535 NORTH DEARBORN STREET • CHICAGO 10, ILLINOIS

Entered as Second Class Matter Jan. 23, 1909, at the Postoffice at Chicago, Under the Act of March 3, 1879. Annual Subscription, $10.00

four reports

attesting to the safety of

'Dexedrine' Sulfate in

obese hypertensives

1

Goodman and Housel (the latter is chief of the Jefferson Hospital Hypertension Clinic, Philadelphia) conducted exhaustive studies of 100 obese hypertensives. They concluded:

- "Prolonged use of oral 'Dexedrine' Sulfate does not affect the long term blood pressure in obese hypertensive patients."
- "'Dexedrine' consistently reduces the appetite . . . "

Goodman, E.L., and Housel, E.L.: Am. J. M. Sc. 227:250 (March) 1954.

2

"There is no apparent effect on hypertension, and the drug can be used . . . in hypertensives with obesity . . . "

Finch, J.W.: J. Oklahoma M.A. 40:119.

3

'Dexedrine' "has been given in the cases where the blood pressure was over 200 systolic and 100 diastolic without any ill effects, and [many of] these patients have obtained . . . a drop in blood pressure."

Ferguson, H. E.: Virginia M. Monthly 76:222

4

Livingston, after treating a series of 49 patients with 'Dexedrine' for 1-5 years reported that the blood pressure remained "essentially unchanged throughout the course of the treatment."

Livingston, S.; Kajdi, L., and Bridge, E.M.: J. Pediat. 32:490.

Dexedrine* Sulfate

dextro-amphetamine sulfate, S.K.F.

Tablets • Elixir • Spansule† capsules

Smith, Kline & French Laboratories, Philadelphia

*T.M. Reg. U.S. Pat. Off.

†T.M. Reg. U.S. Pat. Off. for S.K.F.'s brand of sustained release capsules.
Patent Applied For

In patients with severe hypertension, therapy should be initiated with relatively small doses and dosage increased gradually until the desired therapeutic effect is achieved.

Instructions to Contributors

Communications regarding editorial management, subscriptions, reprints, etc., should be addressed to Specialty Journals, American Medical Association, 535 North Dearborn Street, Chicago 10.

Articles, book reviews, and other materials for publication should be addressed to the Chief Editor of the Specialty Journal concerned. Articles are accepted for publication on condition that they are contributed solely to that journal.

An original typescript and the first carbon of an article should be provided; it must be double or triple spaced on one side of a standard size page, with at least a 1-inch margin at each edge. An article in English by a foreign author should be accompanied by a draft in the author's mother tongue. Improvised abbreviations should be avoided.

The main title of an article may not contain more than ninety characters and spaces; a subtitle may be of any length. The subtitle should be sufficiently detached from the main title that a punctuation mark as strong as a colon can be used in the Table of Contents to separate it from the main title; it must not begin with "with."

The author's name should be accompanied by the highest academic or medical degree which he holds. If academic connections are given for one author of an article, such connections must be given for all other authors of the article who have such connections.

Typographic considerations necessitate that the first paragraph of an article contain not fewer than thirty words. A Case Report must be preceded by an introductory paragraph containing at least thirty words before the details of the case are given.

Material quoted from another publication must be quoted exactly if the original is in English—spelling, capitalization, punctuation, etc., unchanged. Material taken largely from another publication must be credited to the original author, whether quoted exactly or merely abstracted. If such material is quoted indirectly, the author must be careful to leave no complete sentence of the original unaltered. Use of uncredited quotations will be sufficient cause for rejection of an article.

Each article should be accompanied by a summary in the present tense, presenting the main points of the article, but in somewhat more generalized terms than in the article itself.

If it is necessary to publish a recognizable photograph of a person, the photograph must be accompanied by written permission of the subject himself if an adult, or of the parents or guardian if a child, to publish his photograph. An illustration which has been published in another publication must be accompanied by written permission from the author and the original publisher to reproduce it in an A. M. A. Specialty Journal.

The maximum illustration allowance is ten illustrations within a total of 100 sq. inches or $100, whichever is of greater advantage to the author. When no restrictions are placed by the author upon cropping, reducing, and grouping, the publisher is often able to use twenty or more illustrations in one article with the $100 allowance. Submit sharp prints of the following sizes, 2½″ wide × 2½″ or 3½″ high, 3½″ wide × 2½″ high, and 5½″ or 7″ wide × 3½″ high, to minimize reduction and/or cropping. Oversized originals should be photographed and a print submitted. Large photomicrograph prints will be reduced in scale unless portions to be cropped are indicated by the author.

Any cut-off marks should be made on the margins or mountings rather than on the illustration itself. Charts and drawings should be in black ink on hard, white paper. Lettering must be large enough to permit necessary reduction. Glossy prints of x-rays are requested. Paper clips should not be used on prints, since their mark shows in reproduction, as does writing on the back of prints with hard lead pencil or stiff pen. Labels should be prepared and pasted to the back of each illustration showing its number, the author's name, an abbreviated title of the article, and top plainly indicated. Charts and illustrations must have descriptive legends, grouped on a separate sheet. Tables must have captions. IT IS PREFERRED THAT ILLUSTRATIONS BE UNMOUNTED.

References to the literature should be numbered in the order in which they are referred to in the text or listed in alphabetical order without numbers. A chronological arrangement, with all entries for a given year alphabetized according to the surname of the first author, may be used if preferred. References should be typed on a special page at end of manuscript. They should conform to the style of the Quarterly Cumulative Index Medicus, and must include, in the order given, name of author, title of article (with subtitle), name of periodical, with volume, page, month—day of month if weekly or biweekly—and year. Names of periodicals should be given in full or abbreviated exactly as in the Quarterly Cumulative Index Medicus. Reference to books must contain, in the order given, name of author, title of book, city of publication, name of publisher, and year of publication. Titles of foreign articles, if originally in a generally known Romance or Germanic tongue, must either all be in English translation or all be in the original language. Titles in other languages must be translated. The author must assume responsibility for the accuracy of foreign titles.

Matter appearing in the A. M. A. Specialty Journals is covered by copyright, but as a rule no objection will be made to its reproduction in a reputable medical journal if proper credit is given. However, the reproduction for commercial purposes of articles appearing in the A. M. A. Specialty Journals, or in any other publications issued by the Association, will not be permitted.

AMERICAN MEDICAL ASSOCIATION

535 North Dearborn Street **Chicago 10**

"A program of treatment for *chronic ulcerative colitis*. . .

. . . is based on the use of 1) AZOPYRINE,* 2) ACTH or cortisone and 3) psychotherapy. "Azopyrine*. . . has been effective in controlling the disease in approximately two-thirds of patients who had previously failed to respond to standard colitis therapy currently in use."

Lester M. Morrison, M.D., Los Angeles, in Rev. Gastroenterology, 20:744 (Oct.) 1953; abstract in J.A.M.A. 153:1580 (Dec. 26) 1953.

* *now available under the name*

ACCEPTED COUNCIL ON PHARMACY AND CHEMISTRY AMERICAN MEDICAL ASSOCIATION

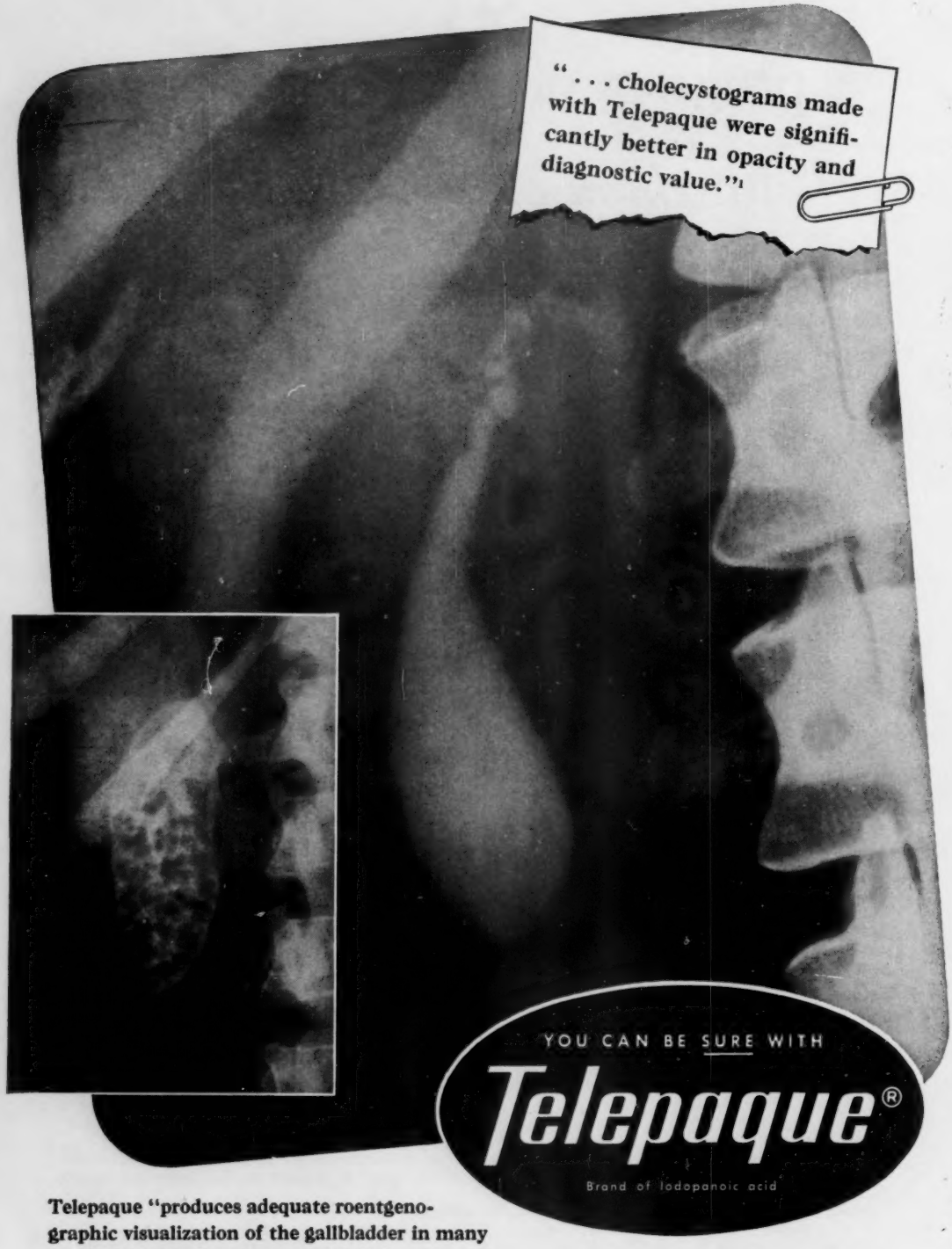
Azulfidine®

BRAND OF SALICYLAZOSULFAPYRIDINE

literature on request from

PHARMACIA LABORATORIES, Inc.

Executive Offices: 270 Park Ave., New York 17, N. Y., Sales Offices: 300 First St., N. E., Rochester, Minn.


"... cholecystograms made with Telepaque were significantly better in opacity and diagnostic value."[1]
YOU CAN BE SURE WITH
Telepaque®
Brand of Iodopanoic acid

Telepaque "produces adequate roentgenographic visualization of the gallbladder in many cases where another compound failed to do so."[2]

Average adult dose: 6 tablets orally. For medium or thin persons under 150 lb., 4 tablets are usually sufficient. Telepaque should be taken with at least one full glass of water.

Winthrop-Stearns INC.
NEW YORK 18, N. Y. WINDSOR, ONT.

1 Abel, M.S., Lomhoff, I.I., and Garcia, C.V.: *Permanente Found. Med. Bull.*, 10:95, Aug., 1952.
2 Lowman, R.M., and Stanley, H.W.: *Connecticut Med. Jour.*, 16:591, Aug., 1952

Telepaque, trademark reg. U. S. & Canada

STUDIES IN IRON TRANSPORTATION AND METABOLISM

VIII. Absorption of Radioiron from Iron-Enriched Bread

RUTH STEINKAMP, M.D.
REUBENIA DUBACH, Ph.D.
and
CARL V. MOORE, M.D., St. Louis

THE INVESTIGATIONS reported below were designed to study the nutritional value of fortifying flour with iron. The four different iron preparations most commonly used in the enrichment program (ferrous sulfate, reduced iron, ferric orthophosphate, and sodium ferric pyrophosphate) were made from radioactive iron (Fe^{59}) of high specific activity and were baked into bread under conditions which closely simulated those employed in the baking industry. Absorption of Fe^{59} from the enriched bread was then measured in human subjects. This kind of evaluation has been long overdue. The original recommendation of the Council on Foods and Nutrition of the American Medical Association [1] emphasized that there obviously would be no nutritional advantage in enriching bread or other food with iron if the added iron were not available for absorption. Yet the iron preparations which have come to be used, with the exception of ferrous sulfate, are certainly not the ones that one would expect to be best absorbed. Practical industrial problems have largely dictated their selection, in spite of observations indicating that solubility, ease of ionization, and the ferrous valence state are properties which lead to the greatest assimilation of iron.* It would seem, therefore, that, of the four iron preparations, ferrous sulfate should be by far the most efficacious, provided the ferrous ion were not oxidized during the baking process. It is, however, one of the least used. In spite of these considerations, no significant difference was found in the amount of iron absorbed when bread was enriched with each of the four iron preparations. Utilization was sufficient to prove the value of the addition.

In an earlier attempt to study the effectiveness of fortifying food with iron, ferric phytate and ferrous sulfate were added to bread in amounts large enough so that subjects with hypochromic microcytic anemia could obtain a therapeutic dose of iron by eating the bread.[4] Reticulocyte responses and hemoglobin regeneration were followed. In two patients, 1 gm. of iron as ferric phytate produced a smaller therapeutic effect than did 0.3 gm. as ferrous sulfate. The method, however, was cumbersome, and the quantity of iron baked into the bread was so large that the method bore little resemblance to actual procedures of the baking industry. Other workers have made comparisons on animals, usually by measuring hemoglobin regeneration in young rats made anemic by a milk diet. Nakamura and Mitchell [5] found that rats utilized sodium iron pyrophosphate, reduced iron, and ferric chloride equally well but that ferric phytate was only 56% as effective as ferric chloride. Street,[6] using the same technique, concluded that the iron of sodium iron pyrophosphate was less than 50% as available for hemoglobin synthesis as was the iron of ferrous sulfate or ferric sulfate, whether baked into bread or given as the salt. Freeman and Burrill [7] reported that

National Cancer Institute Trainee (Dr. Steinkamp).

From the Department of Internal Medicine, Washington University School of Medicine.

Read at the 18th Annual Meeting of the American Institute of Nutrition, Atlantic City, N. J., April 15, 1954.

Supported in part by Research Grant No. H22 from the National Heart Institute, United States Public Health Service, Department of Health, Education, and Welfare, and in part by the Bill Burns Research Fund.

* References 2 and 3.

anemic rats utilized iron in the following descending order: ferric chloride > ferric orthophosphate > reduced iron > sodium iron pyrophosphate. Results were the same whether the salts were fed alone or baked into bread. Blumberg and Arnold[8] compared, under similar experimental conditions, the absorption by anemic rats of ferrous sulfate, ferrous chloride, and ferric orthophosphate, incorporated into bread at different levels; ferrous sulfate and ferrous chloride were each four to five times as effective as ferric orthophosphate. These various results, however, cannot serve as an index of absorption in man, because a species difference in iron absorption is known to exist.[2]

The four iron preparations used for the enrichment of baked goods are, in descending order of frequency: ferric orthophosphate, reduced iron powder, ferrous sulfate, and sodium ferric pyrophosphate.[9] Ferric orthophosphate is used to enrich bread at the bakery, where it is added to the dough in the form of an enrichment wafer with thiamine, riboflavin, and nicotinic acid. Ferrous sulfate is used to a lesser extent in the same fashion. Reduced iron powder is used principally in the enrichment of family flour at the mill. Sodium ferric pyrophosphate is used to a limited extent in certain flour mixtures. Iron phytate is no longer used. Enrichment provides an extra 9 to 12 mg. per pound of flour and 6 to 8 mg. per pound of bread.

PLAN OF THE INVESTIGATION

The fortified bread was eaten in the morning as breakfast, after an overnight fast, by 26 healthy male medical students between the ages of 23 and 32 years, by 6 healthy women 21 to 28 years of age, and by 3 patients with hypochromic microcytic anemia. The feces of all subjects were collected, so that the unabsorbed radioactivity could be measured. In addition, determination was made of the Fe^{59} which appeared in the circulating blood as newly synthesized hemoglobin. After several weeks, one of several types of control study was done: (*a*) the same amount of Fe^{59} preparation was given alone or (*b*) with as much ordinary bread as had been eaten in the Fe^{59}-fortified form, or (*c*) the same Fe^{59} bread was taken with a supplement of ascorbic acid.

MATERIAL AND METHODS

One of the principal problems was to synthesize the four iron preparations in pure form, with Fe^{59} of high specific activity, in the small amounts required so that radioactivity would not be wasted. The problem was solved when simplified techniques for these syntheses were made available to us by Merck & Company, Inc.; the methods are given in the Appendix to this paper. The syntheses of the radioactive materials were actually made by the Abbott Laboratories, Department of Radioactive Pharmaceuticals, with materials obtained under allocation from the Isotopes Division of the Atomic Energy Commission.† Ferrous sulfate was supplied as a solution, with a specific activity of 1,710 μc. per milligram of iron. The other three preparations were supplied as powders and had specific activities of 41 to 141 μc. per milligram of iron. The iron and phosphorus content of the radioactive ferric orthophosphate was determined before the salt was used and was found to agree with the formula, $FePO_4 \cdot 4H_2O$. In the case of the radioactive sodium ferric pyrophosphate, the iron, phosphorus, and sodium were determined. A high ratio of P to Fe and an excess of Na indicated that the double pyrophosphate, $2(Na_4P_2O_7)\ Fe_4(P_2O_7)_3$ was contaminated with $Na_4P_2O_7 \cdot 10\ H_2O$. Inasmuch as the amount of radioactive sodium iron pyrophosphate used for enrichment was based on the determined iron content, the excess sodium pyrophosphate did not affect the usefulness of the salt as a source of iron.

For each experiment two 19 oz. (538.7 gm.) loaves of bread were baked under commercial conditions in the experimental bakery of the Anheuser-Busch Brewing Company.‡ The sponge was prepared from 700 gm. of unenriched white flour. Instead of the enrichment wafer which the baker normally added to the sponge, he used an iron-free vitamin powder§ plus the radioactive iron, at a level of 142 mg. of vitamin mixture and 12 mg. of

† Drs. Charles Rosenblum, H. L. Pfluger, and Augustus Gibson, of Merck & Company, Inc., supplied the methods of synthesis, and Dr. D. L. Tabern and Mr. Thomas Lahr, of Abbott Laboratories, prepared the Fe^{59} salts.

‡ Dr. Robert Sumner, of the Central Research Department of Anheuser-Busch, arranged for the baking of the bread enriched with the four forms of Fe^{59} by Mr. Russell Gaydos.

§ Dr. John F. Mahoney, of Merck & Company, Inc., supplied us with a vitamin mixture, prepared without iron, which corresponded to the vitamin mixture used commercially. One-half ounce is added to 100 lb. (45 kg.) of flour to supply 1.90 mg. thiamine hydrochloride, 1.15 mg. riboflavin, and 13.70 mg. nicotinic acid per pound (0.45 kg.) of flour.

elemental iron per pound (0.45 kg.) of flour. The ferrous sulfate was added as a solution to the sponge. The ferric orthophosphate and sodium ferric pyrophosphate were added as suspensions in water. The reduced iron, finely powdered, was thoroughly mixed with the dry flour. Multiple sampling of the loaves showed a fairly even distribution of the isotope throughout the bread (Table 1).

The radioactivity of the iron preparations used for enrichment provided 30 to 75 μc. Fe^{59} per loaf except in the experiment with ferric orthophosphate, when 450 μc. was added. Since the Fe^{59} salts were of high specific activity, chemically pure carrier salt was used to bring the level of iron to 12 mg. per pound (0.45 kg.) of flour. The iron content of the bread varied from 0.022 to 0.037 mg. Fe per gram of wet weight. In every instance there were appreciable amounts of iron from natural sources present, so that the iron found was considerably more than the iron which had been added.

The loaves were sliced by a mechanical slicer. Portions of approximately 100 gm. (four slices) were weighed to the nearest 10 mg. and wrapped in Parafilm until they were eaten. The end crusts were always discarded. Single slices, at different positions in the loaf, were weighed at the same time and were assayed for iron content and for radioactivity.

Each subject ate the labeled bread with butter, after a 10- to 14-hour fast. Water was allowed, as desired. Quantitative collections of feces were made until a day's specimen showed less than 1% of the radioactivity of the dose. Blood specimens were drawn at three- or four-day intervals for determination of the radioactive iron in the hemoglobin. The total amount of the isotope circulating in the hemoglobin was calculated from the red cell mass. In six cases this was determined, at the end of the experiment, by the radioactive chromium technique [10]; in the others the blood volume was estimated to be 80 ml. per kilogram of body weight.

For the assay of radioactive iron in feces, the gamma rays were measured with a well-type scintillation counter.‖ Several days' specimens were mixed with water in a mechanical blender. After the total homogenate was weighed, triplicate samples were weighed in 4 ml. vials and counted in the scintillation well counter. The radioactivity was related to that of standards (prepared in triplicate) from the enriched bread. In the first ferrous sulfate absorption study, aliquots of 8 to 55 gm. of feces homogenate were dry ashed before counting. In all the other studies, approximately 2 gm. aliquots of the mixed feces were counted in the liquid state.

Since the amounts of iron which were absorbed from the bread were small, the radioactive iron of the blood was measured with a Geiger counter, for greater sensitivity. A 10 ml. aliquot of whole blood was digested and electroplated, as previously described,¶ and was counted with an end-window beta counter. The radioactivity was related to that of standards prepared from the enriched bread.

Multiple blood samples were taken from each subject in order to verify the fact that the radioiron in the blood had reached a constant level. At least two weeks were allowed to elapse before the second test meal was given. Just before the second dose, a blood specimen was taken for determination of the "base line" radioactivity, and this value was deducted from the observed radioactivity of subsequent blood samples.

On each subject, red blood cell counts, hemoglobin estimations, and packed cell volumes were determined at the beginning of the study and several times subsequently.

TABLE 1.—*Radioactivity of Samples Taken from Different Parts of a Loaf of Bread Enriched with Radioactive Ferrous Sulfate*

Sample	Wet Wt., Gm.	Counts/Sec. Above Background *	Net Counts/ Sec./Gm.	Average of Group, Counts/ Sec./Gm.	% Deviation from Average
Crust a	0.630	140.7	224	230 †	— 2.6
Crust b	0.426	94.3	221	230	— 3.9
Crust c	0.252	65.5	260	230	+13.0
Crust d	0.508	107.5	212	230	— 7.8
Crust e	0.409	96.0	235	230	+ 2.2
Crumb 1	0.940	214.6	229	206	+11.2
Crumb 2	1.140	210.1	184	206	—10.7
Crumb 3	0.920	184.5	201	206	— 2.4
Crumb 4	0.536	94.3	179	206	—13.1
Crumb 5	0.424	88.1	208	206	+ 1.0
Crumb 6	0.720	157.7	219	206	+ 6.3
Crumb 7	0.370	72.0	195	206	— 5.3
Crumb 8	0.430	98.9	230	206	+11.6

* Aliquots of the fresh bread, taken from different parts of the loaf, were counted in the well scintillation counter.
† The somewhat higher concentration of Fe^{59} in the crust was attributed to its lower water content.

‖ References 11 and 12.
¶ References 2 and 13.

TABLE 2.—*Absorption of $Fe^{59}SO_4$ from Bread and from the Free Salt by Healthy Subjects*

Subject	Age, Yr.	Sex	Body Wt., Kg.	Form of $Fe^{59}SO_4$	Fe, Mg.	Counts/ Min.†	% of Dose of Fe^{59}		
							In Blood	In Feces	Recovered
Group I									
C. N.	24	M	80.5	Fe^{59} bread, 94 gm.	3.5	1,130,000	0.8	94.8	95.6
				Salt	4.0	1,500,000	2.3	98.5	100.3
M. M.	23	M	59.5	Fe^{59} bread, 91 gm.	3.4	1,090,000	3.2	96.7	99.9
				Salt	4.0	1,500,000	14.7	84.5	99.2
J. G.*	26	M	68	Fe^{59} bread, 86 gm.	3.2	1,030,000	3.7	89.7	93.4
				Salt	4.0	1,500,000	18.7	78.5	97.2
R. V.*	24	M	94	Fe^{59} bread, 97 gm.	3.6	1,160,000	11.2	86.2	97.4
				Salt	4.0	1,500,000	14.0	83.2	97.2
N. L.	21	F	47	Fe^{59} bread, 93 gm.	3.5	1,120,000	3.0	95.4	98.4
				Salt	4.0	1,500,000	14.5	80.3	94.8
Group II									
D. T.	23	M	85	Fe^{59} bread, 102 gm.	2.9	2,040,000	1.0	92.5	93.5
				Salt + bread	2.9	2,500,000	0.7	100.0	100.7
F. K.	23	M	84.5	Fe^{59} bread, 111 gm.	3.2	2,200,000	5.3	85.4	90.8
				Salt + bread	3.2	2,500,000	6.9	89.3	96.2
O. L.	30	M	71	Fe^{59} bread, 82 gm.	2.4	1,600,000	4.8	96.9	101.7
				Salt + bread	2.4	2,500,000	6.9	88.8	95.7
J. P.	23	M	67	Fe^{59} bread, 91 gm.	2.6	1,839,000	4.8	95.2	100.0
				Salt + bread	2.6	2,500,000	1.8	94.3	96.1
Group III									
D. O'G.	28	F	61	Fe^{59} bread, 95 gm.	3.5	1,140,000	7.6	92.4	100.0
D. R.	26	M	85	Fe^{59} bread, 95 gm.	3.5	1,140,000	1.7	94.9	96.6

* Blood volume determined by radiochromium technique. The blood volumes of the other subjects were estimated on the basis of the body weight.

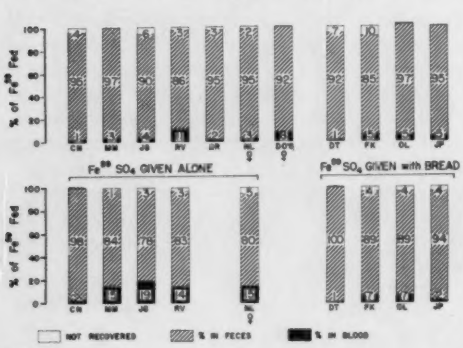
† The radioactivity is expressed in counts per minute given by the scintillation counter at the beginning of the experiment.

RESULTS

I. Absorption of Radioactive Iron from Bread by Healthy Volunteers

A. Ferrous Sulfate.—Two batches of bread enriched with radioactive ferrous sulfate were fed to 11 normal volunteers (Table 2 and Fig. 1). The subjects were divided into three groups. The first group (four men and one woman) was given, in a control experiment, the same amount of labeled ferrous sulfate (in solution) which each subject had consumed in the enriched bread; the second group (four men) was given, in the control experiment, ferrous sulfate solution plus a supplement of four slices of commercial bread. The third group (one man and one woman) was given, in the control experiment, a second 100 gm. portion of the labeled enriched bread plus a supplement of 1 gm. of ascorbic acid (Table 6 and Fig. 6).

Fig. 1.—Upper row, recovery of Fe^{59} in blood and feces of normal subjects after ingestion of bread enriched with radioactive ferrous sulfate. Lower row, each column represents a control experiment on the person shown immediately above it. In the first group $Fe^{59}SO_4$ was given alone; in the second group $Fe^{59}SO_4$ was given with a bread supplement.


ABSORPTION OF Fe59SO4 FROM BREAD BY HEALTHY SUBJECTS (TOP ROW)
COMPARED WITH ABSORPTION OF THE INORGANIC SALT (BOTTOM ROW)
% of Fe59 Fed
Fe59 SO4 GIVEN ALONE
Fe59 SO4 GIVEN with BREAD
NOT RECOVERED
% IN FECES
% IN BLOOD

In Figure 1 and Table 2 it may be seen that the amount of Fe^{59} which was recovered in the blood and feces varied from 90 to 102%. The error of the method is sufficiently great that when 10% of the radioactivity of a test dose is unaccounted for it is impossible to determine whether the deficit is in the assay or is due to absorption of iron that is not utilized for hemoglobin synthesis. Error in the estimation of blood volume could not account for the difference, because when only 10% of the dose appears in circulating hemoglobin, a variation of 20% in blood volume would influence the result very little. At any rate, in describing the results it is more con-

TABLE 3.—*Absorption of Reduced Iron Powder from Bread and from the Free Powder by Healthy Subjects*

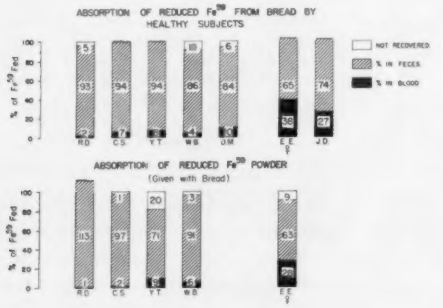
Subject	Age, Yr.	Sex	Body Wt., Kg.	Form of Reduced Fe^{59}	Fe, Mg.	Counts/ Min.*	% of Dose of Fe^{59}		
							In Blood	In Feces	Recovered
R. D.	26	M	72	Fe^{59} bread, 108 gm.	2.5	1,350,000	2.3	93.3	95.6
				Powder + bread	3.3	815,000	0.5	113.3	113.8
C. S.	24	M	74	Fe^{59} bread, 113 gm.	2.6	1,410,000	7.2	94.2	101.4
				Powder + bread	3.0	742,000	2.4	96.7	99.1
Y. T.	23	M	74.5	Fe^{59} bread, 101 gm.	2.4	1,260,000	8.1	93.7	101.8
				Powder + bread	2.6	640,000	9.6	70.8	80.4
W. B.	24	M	85	Fe^{59} bread, 105 gm.	2.5	1,310,000	4.7	85.8	90.5
				Powder + bread	2.2	1,230,000	5.9	90.6	96.5
D. M.	23	M	75	Fe^{59} bread, 112 gm.	2.6	1,400,000	10.1	84.3	94.4
E. E.	25	F	55	Fe^{59} bread, 111 gm.	2.6	1,382,000	37.9	64.9	102.8
				Powder + bread	3.3	1,840,000	27.5	63.3	90.8
J. D.	23	M	72	Fe^{59} bread, 102 gm.	2.4	1,270,000	26.6	73.7	100.3

* The radioactivity is expressed in counts per minute given by the scintillation counter at the beginning of the experiment.

venient to refer specifically to the per cent of the dose which appeared as circulating hemoglobin. From 0.8 to 11.2% of the Fe^{59} in bread was absorbed and utilized for hemoglobin. When ferrous sulfate was given alone, greater absorption and utilization were found (2.3 to 18.7%); when, however, free ferrous sulfate was given with a bread supplement, the absorption of the Fe^{59} was of the same order as when the enriched bread was given. When bread enriched with ferrous sulfate was fed to two volunteers with a supplement of ascorbic acid (Table 6 and Fig. 6), absorption and utilization were increased from 1.7 to 12.0 and from 7.6 to 28.8%, respectively.

B. Reduced Iron.—Bread enriched with reduced Fe^{59} was eaten by seven healthy subjects (six men and one woman) (Table 3 and Fig. 2). Recovery of the isotope in the blood and feces ranged from 90 to 103%. Five persons absorbed and utilized 10% or less of the iron of the bread; the absorption of two others was conspicuously higher than that of the group. J. D., a man, and E. E., a woman, absorbed and utilized 26.6 and 37.9%, respectively, of the Fe^{59} in the bread. The high level of absorption by these subjects (in both of whom the mean corpuscular volume and mean corpuscular hemoglobin concentration were normal) suggested that their iron stores might have been low. J. D. had been a blood donor twice during the year; his serum iron, however, was 0.097 mg. per 100 cc. E. E. had a history of menorrhagia and was found to have a serum iron of 0.050 mg. per 100 cc. In a control experiment five of the subjects took reduced iron powder, with a supplement of bread and butter; they absorbed amounts of iron similar to those absorbed from the fortified bread. A sixth subject, D. M. (Table 6 and Fig. 6) ate a portion of the reduced iron bread with an ascorbic acid supplement; 31% of the iron appeared in his circulating hemoglobin as compared with 10% when the bread was given without ascorbic acid.

Fig. 2.—Upper row, recovery of Fe^{59} in blood and feces of normal subjects after ingestion of bread enriched with radioactive iron powder. Lower row, Each column represents a control experiment on the person shown immediately above it.



C. Ferric Orthophosphate.—The absorption of labeled ferric orthophosphate from bread was measured in four men and two women (Table 4 and Fig. 3). Total recovery of Fe^{59} varied between 93 and 103%. The values for the amounts absorbed and utilized

TABLE 4.—*Absorption of Ferric Orthophosphate from Bread and from the Free Salt by Healthy Subjects*

Subject	Age, Yr.	Sex	Body Wt., Kg.	Form of $Fe^{59}PO_4$	Fe, Mg.	Counts/ Min.*	% of Dose of Fe^{59} In Blood	% of Dose of Fe^{59} In Feces	% of Dose of Fe^{59} Recovered
W. C.	26	M	72	Fe^{59} bread, 103 gm.	2.9	15,400,000	2.3	94.5	96.8
V. C.†	24	M	74	Fe^{59} bread, 110 gm.	3.1	16,500,000	1.9	91.0	92.9
				Salt + bread	2.1	15,000,000	3.6	97.7	101.3
W. P.†	24	M	79	Fe^{59} bread, 112 gm.	3.1	16,800,000	12.0	82.8	94.8
				Salt + bread	2.1	15,000,000	10.4	84.4	94.8
H. S.	23	M	68	Fe^{59} bread, 97 gm.	2.7	14,600,000	2.4	96.0	98.4
				Salt + bread	2.0	13,800,000	5.9	91.8	97.7
S. K.†	25	F	58	Fe^{59} bread, 87 gm.	2.4	13,000,000	10.1	93.1	103.2
				Salt + bread	1.0	7,500,000	3.5	64.4	67.9
E. E.†	22	F	58	Fe^{59} bread, 78 gm.	2.2	11,750,000	3.5	89.9	93.4

* The radioactivity is expressed in counts per minute given by the scintillation counter at the beginning of the experiment.

† Blood volume determined by radiochromium technique. The blood volumes of the other subjects were estimated on the basis of the body weight.

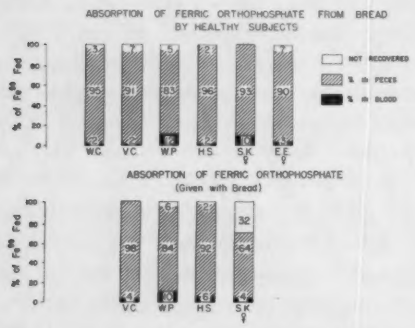

ABSORPTION OF FERRIC ORTHOPHOSPHATE FROM BREAD BY HEALTHY SUBJECTS
% of Fe59 Fed
NOT RECOVERED
% in FECES
% in BLOOD
WC VC WP HS SK EE
ABSORPTION OF FERRIC ORTHOPHOSPHATE (Given with Bread)
VC WP HS SK

Fig. 3.—Upper row, recovery of Fe^{59} in blood and feces of normal subjects after ingestion of bread enriched with radioactive ferric orthophosphate. Lower row, each column represents a control experiment on the person shown immediately above it.

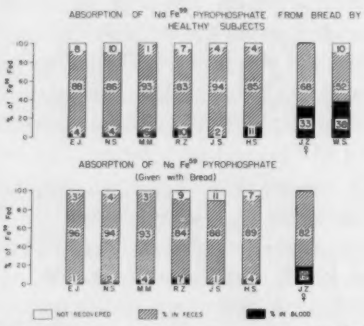

ABSORPTION OF Na Fe59 PYROPHOSPHATE FROM BREAD BY HEALTHY SUBJECTS
% of Fe59 Fed
EJ NS MM RZ JS HS JZ WS
ABSORPTION OF Na Fe59 PYROPHOSPHATE (Given with Bread)
EJ NS MM RZ JS HS JZ
NOT RECOVERED
% IN FECES
% IN BLOOD

Fig. 4.—Upper row, recovery of Fe^{59} in blood and feces of normal subjects after ingestion of bread enriched with radioactive sodium ferric pyrophosphate. Lower row, each column represents a control experiment on the person shown immediately above it.

TABLE 5.—*Absorption of Sodium Ferric Pyrophosphate from Bread and from the Free Salt by Healthy Subjects*

Subject	Age, Yr.	Sex	Body Wt., Kg.	Form of $Na_8Fe^{59}_4(P_2O_7)_5$	Fe, Mg.	Counts/ Min.*	% of Dose of Fe^{59} In Blood	% of Dose of Fe^{59} In Feces	% of Dose of Fe^{59} Recovered
E. J.	25	M	71	Fe^{59} bread, 108 gm.	3.3	1,290,000	3.5	88.2	91.7
				Salt + bread	3.3	1,560,000	1.0	95.6	96.6
N. S.	27	M	74	Fe^{59} bread, 126 gm.	3.9	1,500,000	3.9	85.8	89.7
				Salt + bread	3.8	1,560,000	2.5	93.5	96.0
M. M.	24	M	59	Fe^{59} bread, 115 gm.	2.5	2,070,000	6.0	93.6	99.6
				Salt + bread	2.6	3,500,000	4.2	92.6	96.8
R. Z.	24	M	74.5	Fe^{59} bread, 111 gm.	3.4	1,325,000	9.6	83.3	92.9
				Salt + bread	3.4	1,370,000	6.8	84.4	91.2
J. S.	32	M	62	Fe^{59} bread, 104 gm.	2.3	1,875,000	1.8	94.0	95.8
				Salt + bread	2.3	3,200,000	0.5	88.2	88.7
H. S.	23	M	75	Fe^{59} bread, 114 gm.	2.5	2,050,000	11.5	85.0	96.5
				Salt + bread	2.5	3,200,000	4.1	89.1	93.2
J. Z.	23	F	57	Fe^{59} bread, 104 gm.	3.1	1,240,000	33.4	67.5	100.9
				Salt + bread	3.1	1,230,000	18.8	81.7	100.5
W. S.	23	M	81	Fe^{59} bread, 124 gm.	3.8	1,480,000	38.2	52.1	90.3

* The radioactivity is expressed in counts per minute given by the scintillation counter at the beginning of the experiment.

for hemoglobin ranged from a low of 2% to a high of 12%. These values are closely comparable to the amounts of iron absorbed and utilized from bread enriched with ferrous sulfate. After an interval of three weeks, four of the volunteers were given ferric orthophosphate powder with a supplement of four slices of commercial bread, with butter. The amounts of Fe^{59} which appeared in the blood ranged from 3.5 to 10.4%. In one of the control experiments the Fe^{59} found in the feces was only 64% of the dose. We interpret this figure as evidence that in this instance the fecal iron recovery was incomplete rather than that 36% of the iron was absorbed. The

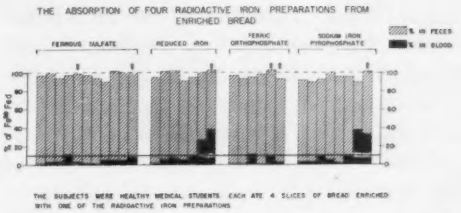

THE ABSORPTION OF FOUR RADIOACTIVE IRON PREPARATIONS FROM ENRICHED BREAD
FERROUS SULFATE
REDUCED IRON
FERRIC ORTHOPHOSPHATE
SODIUM IRON PYROPHOSPHATE
% IN FECES
% IN BLOOD
% OF Fe59 Fed
THE SUBJECTS WERE HEALTHY MEDICAL STUDENTS. EACH ATE 4 SLICES OF BREAD ENRICHED WITH ONE OF THE RADIOACTIVE IRON PREPARATIONS.

Fig. 5.—Comparison of the absorption of Fe^{59} after ingestion of bread enriched with four different forms of radioiron. A horizontal line has been drawn arbitrarily at the level of 10% utilization in the blood.

(one, a woman) showed absorption and utilization of over 30% of the isotope (W. S. and J. Z., Table 5 and Fig. 4). The other

TABLE 6.—*Effect of Ascorbic Acid on the Absorption of Four Iron Preparations from Enriched Bread by Healthy Subjects*

Subject	Age, Yr.	Sex	Body Wt., Kg.	Form of Fe^{59} Used for Enrichment	Fe, Mg.	Counts/ Min.*	% of Dose of Fe^{59} In Blood	In Feces	Recovered
D. R.	26	M	85	$Fe^{59}SO_4$ bread, 95 gm.	3.5	1,140,000	1.7	94.9	96.6
				Same bread, 69 gm. + ascorbic acid †	2.6	580,000	12.0	89.1	101.1
D. O'G.	28	F	61	$Fe^{59}SO_4$ bread, 95 gm.	3.5	1,140,000	7.6	92.4	100.0
				Same bread, 68 gm. + ascorbic acid †	2.5	570,000	28.8	74.3	103.1
D. M.	23	M	75	Reduced Fe^{59} bread, 112 gm.	2.6	1,400,000	10.1	84.3	94.4
				Same bread, 107 gm. + ascorbic acid †	2.5	915,000	31.5	69.3	100.8
W. C.	26	M	72	$Fe^{59}PO_4$ bread, 103 gm.	2.9	15,400,000	2.3	94.5	96.8
				Same bread, 104 gm. + ascorbic acid †	2.9	4,750,000	13.8	83.8	97.6
E. E.‡	22	F	58	$Fe^{59}PO_4$ bread, 78 gm.	2.2	11,750,000	3.5	89.9	93.4
				Same bread, 76 gm. + ascorbic acid †	2.1	3,440,000	14.8	83.7	98.5
W. S.	23	M	81	$Na_8Fe^{59}_4(P_2O_7)_5$ bread, 124 gm.	3.8	1,480,000	38.2	52.1	90.3
				Same bread, 140 gm. + ascorbic acid †	4.3	1,200,000	67.0	39.1	106.1

* The radioactivity is expressed in counts per minute given by the scintillation counter at the beginning of the experiment.
† One gram of ascorbic acid, dissolved in 50 ml. of water, was taken immediately after the bread.
‡ Blood volume determined by radiochromium technique. The blood volumes of the other subjects were estimated on the basis of the body weight.

amount found in the blood was 3.5%. Of this group, one man and one woman ate a second portion of the ferric orthophosphate bread with an ascorbic acid supplement (Table 6 and Fig. 6). The amounts of iron absorbed and utilized rose from 2 to 14% in the man and from 3.5 to 15% in the woman.

D. Sodium Ferric Pyrophosphate.—Bread enriched with radioactive sodium ferric pyrophosphate was baked twice; portions were eaten by eight volunteers (Table 5 and Fig. 4). The radioiron recovered from the feces and the peripheral blood varied from 90 to 101% of the Fe^{59} ingested. Two persons

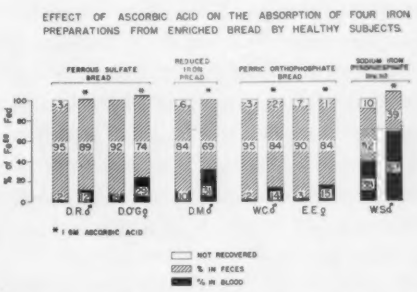


Fig. 6.—The left column of each pair shows the recovery of Fe^{59} in blood and feces after the ingestion of bread enriched with a radioiron salt. The right column shows a control experiment in which the same subject ate bread enriched with the same salt plus a supplement of ascorbic acid.

six absorbed and utilized between 1.8 and 11.5% of the iron given. In a control experiment in which free sodium ferric pyrophosphate was given with bread and butter, their utilization ranged from 0.5 to 6.8%; J. Z. absorbed 19%. W. S., who had absorbed 38% of the iron from the enriched bread, was given a second portion of the bread with a gram of ascorbic acid (Table 6 and Fig. 6). His absorption rose to over 60%. Both W. S. and J. Z. had shown normal hemoglobin levels and red corpuscular constants. However, W. S. was found to have served as a blood donor at intervals of two or three months for over a year. His serum iron level was 0.049 mg. per 100 cc. J. Z. had a serum iron level of 0.062 mg. per 100 cc. The absorption of over 30% of the pyrophosphate iron by these two persons was probably due to their low iron reserves rather than to the form of the salt.

Figure 5 summarizes the results of the absorption of the four radioactive iron preparations from enriched bread. A line has been drawn arbitrarily at the level of 10% utilization in the blood. Only four of the 32 healthy subjects absorbed and utilized significantly more than 10% of the iron. When the values for the other 28 subjects are compared, no difference can be observed in the availability of the four salts.

II. Effect of Ascorbic Acid on Absorption of Iron from Bread

The effect of ascorbic acid in furthering the absorption and utilization of iron from bread enriched with each of the four preparations is summarized in Table 6 and Figure 6. Two volunteers who ate ferrous sulfate bread, one who ate reduced iron bread, two who ate ferric orthophosphate bread, and one who ate pyrophosphate bread were each given a second test meal of the same bread with ascorbic acid. One gram of ascorbic acid, dissolved in 50 ml. of water, was taken immediately after the bread. In every case, absorption and utilization of the iron were increased when ascorbic acid was given. It is significant that ascorbic acid, which presumably promotes absorption by its reducing action, increased the absorption of iron from the breads to which ferrous iron and metallic iron had been added just as much as it increased the absorption of iron from the breads fortified with the ferric salts.

Table 7.—*Absorption of Three Radioactive Iron Salts from Bread by Patients with Untreated Hypochromic Anemia, Compared with Their Absorption of the Free Salt*

Subject	Age, Yr.	Sex	Body Wt., Kg.	Form of Fe^{59} Used for Enrichment	Fe, Mg.	Counts/ Min.*	% of Dose of Fe^{59}		
							In Blood	In Feces	Recovered
C. M.	19	F	52	$Fe^{59}SO_4$ bread, 79 gm.	2.9	1,700,000	44.9	63.0	107.9
				Salt + bread	2.3	740,000	68.1	58.9	117.0
L. M.	42	F	66.5	$Fe^{59}PO_4$ bread, 52 gm.	1.5	615,000	63.8	.... †	....
				Salt + bread	1.1	600,000	29.0	.... †	....
E. O.	48	F	83	$Na_8Fe^{59}_4(P_2O_7)_8$ bread, 105 gm.	3.2	805,000	57.3	56.4	113.7
				Salt + bread	0.7	652,000	0	99.1	99.1

* The radioactivity is expressed in counts per minute given by the scintillation counter at the beginning of the experiment.
† Incomplete fecal collections.

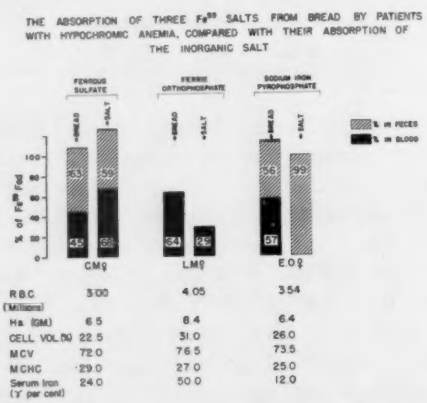


Fig. 7.—Recovery of Fe^{59} in blood and feces of patients with hypochromic anemia after ingestion of bread enriched with three different radioiron salts. The left column of each pair shows absorption of radioiron from bread; the right column, absorption of the free salt.

III. Absorption of Iron from Enriched Bread and from Inorganic Salts by Three Patients with Hypochromic Anemia

Three patients with hypochromic anemia due to blood loss ate portions of bread enriched with three different radioactive iron salts. The results (Table 7 and Fig. 7) are less complete than in the case of the normal subjects. In C. M. and E. O., 108 and 114% of the isotope was accounted for in the blood and feces. The third patient failed to collect the specimens. With each of the enrichment salts, excellent absorption and utilization occurred. The control experiments, in which the free salt was given with a bread supplement, show a somewhat better absorption of ferrous sulfate when it was given as the salt than when incorporated in bread, and a somewhat poorer absorption of ferric phosphate than of ferric phosphate bread. When free sodium ferric pyrophosphate was given, the efficiency of absorption could not be adequately measured because the patient developed diarrhea.

These three experiments show clearly that iron-deficient subjects are able to absorb iron very efficiently from enriched bread.

COMMENT

The equal effectiveness of the four forms of iron used for enrichment is surprising. On the basis of studies of the absorption of inorganic iron salts it was anticipated that ferrous sulfate would be better absorbed than ferric orthophosphate and sodium ferric pyrophosphate, which are (1) soluble only with difficulty and (2) in the ferric valence state. Chemists who have determined the valence state of iron in enriched bread by extraction procedures have found that during the baking process ferrous sulfate is converted partially to the ferric state.# The fact that metallic iron was as well utilized as the other three salts recalls the suggestion of Nakamura and Mitchell [5] that an important source of dietary iron is contaminating particles from iron milling machines.

Mahoney, J. F.: Personal communication to the authors.

The comparatively low level of absorption by all the subjects except those with low iron stores is also of interest. In these experiments only 2 to 4 mg. of iron were given in the test meal, compared to 60 to 80 mg. in earlier studies with inorganic salts.[2] More complete assimilation of the small dose might have been expected. An explanation for the low level of absorption is suggested by the experiments in which ferrous sulfate was fed with and without bread. The fact that a greater percentage of iron from free ferrous sulfate was absorbed when the salt was fed alone than when it was fed with a bread supplement suggests that the presence of bread in the stomach decreased absorption of the Fe^{59}, perhaps because of its phytate content [14] or simply because of its bulk. Sharpe and coworkers found by the radioiron technique that absorption of iron varies with the solid content of the test meal.[15] The amounts of iron which were absorbed from the enriched bread are comparable to the amounts of iron which were absorbed from foods tagged with the radioactive isotope,[16] when the level of iron in the test meal was 2 to 6 mg.

The amount of iron which must be assimilated per day in order to maintain a positive iron balance, as estimated from data on iron excretion, is probably about 1 mg. for men and 1.5 to 2.0 mg. for women. Since normal subjects absorb from 1 to 12% of the iron in enriched bread, the ingestion of six to eight slices (150 to 200 gm.) should result in the retention of from 0.04 to 0.8 mg. of iron. The upper portion of this range would provide a major fraction of the daily requirement. What effect other foods eaten with the bread would have on absorption is problematical; greater solid content of the meal might decrease assimilation,[15] while a high reducing effect of any of the other foods would augment it.[16] Persons with iron deficiency anemia, and possibly even those with normal hemoglobin values but suboptimal iron stores, would probably absorb more than a milligram of iron from eight slices (200 gm). These figures are admittedly based on the results of acute experiments, but there

is no reason to believe that prolonged periods of observation would have given different values. The data provide convincing evidence of the nutritional effectiveness of enriching flour or bread with iron.

SUMMARY

When bread enriched with radioactive ferrous sulfate, reduced iron, ferric orthophosphate, and sodium ferric pyrophosphate was fed to 32 healthy men and women, 28 of the subjects absorbed and utilized between 1 and 12% of the iron, regardless of the form of iron added. The other four subjects assimilated from 26 to 38% of the Fe,[89] but there was reason to suspect that their iron stores were suboptimal in each instance.

Ferrous sulfate baked into bread was absorbed less well than when the free salt was given alone to fasting subjects. When, however, free ferrous sulfate was fed with a bread supplement, absorption of the iron was comparable to absorption from the tagged bread.

When radioactive reduced iron powder, ferric orthophosphate, or sodium ferric pyrophosphate was given with a bread supplement, the level of absorption was comparable to that from the tagged bread.

When bread tagged with the four radioiron preparations was fed with a supplement of ascorbic acid to six healthy subjects, iron absorption was increased two to three times.

When three iron-deficient patients ate bread enriched with radioactive ferrous sulfate, ferric orthophosphate, and sodium ferric pyrophosphate, they absorbed 45 to 64% of the iron taken.

The iron added to bread in the food fortification program is a significant source of iron in human nutrition.

APPENDIX*

Methods of Synthesizing Radioactive Iron Salts on a Small Scale

Methods have been developed for preparing, on a small scale, radioactive ferrous sulfate, ferric orthophosphate, sodium iron pyrophosphate, and reduced (metallic) iron. All reactions are carried out in a single centrifuge tube, starting with 15 mg. of radioactive iron in a stock solution of N HCl. The degree of purity of the preparations is indicated by the analyses given in Tables I to IV.

Table I.—*Ferrous Sulfate Preparation*

	Analysis			Yield	
Source	% Fe	% S	Fe/S	Mg. Product	% *
Trial runs	32.55	18.3	1.78	46.0	99.9
	32.14	18.1	1.72	45.0	96.6
	31.82	19.5	1.64	46.0	97.8
	31.75	18.9	1.68	45.0	95.4
Theoretical $FeSO_4.1H_2O$	32.8	18.9	1.74		

* Based on 15 mg. Fe initially.

Table II.—*Ferric Phosphate Preparation*

	Analysis			Yield	
Source	% Fe	% P	Fe/P	Mg. Product	% *
Trial runs	25.7†	16.5	1.56	53.9	92.4
	25.5†	16.5	1.54	45.9	78.2
	25.6‡	17.4	1.47	49.9	85.3
	25.1‡	18.7	1.34	59.9	100.2
Commercial products	24.3	17.1	1.42	....	....
	29.7	17.2	1.73	....	....
Theoretical $FePO_4.4\ H_2O$	25.0	13.9	1.80	....	....

* Based on 15.0 mg. Fe initially.
† Final washing with water.
‡ Final washing with aqueous ethanol.

Part I.—*Precipitation of Ferric Hydroxide*

1. Transfer 15 ml. of stock radioactive iron solution (containing 1 mg. of iron per milliliter of 1 N HCl) to a 50 ml. centrifuge tube fitted with a 24/40 female ground-glass joint at the top.

2. Convert any ferrous ion to ferric by addition of two drops of 30% hydrogen peroxide (Superoxol). Remove excess hydrogen peroxide by boiling.

3. After cooling, add 2.5 ml. of 6 N ammonium hydroxide.

4. Sedimentate the precipitated ferric hydroxide by centrifugation, and decant the supernatant liquid.† Wash the precipitate free of chloride ion with four successive 15 ml. portions of distilled water, each followed by centrifugation and decantation.

* This Appendix was written by Drs. Charles Rosenblum and H. L. Pfluger, Research Laboratories, Merck & Company, Inc.

† It is suggested that this and subsequent wash waters be filtered to recover small amounts of uncentrifuged radioactive iron compound.

PART II.—*Preparation of Ferrous Sulfate from Ferric Hydroxide*

1. Suspend the washed ferric hydroxide (prepared in a 50 ml. centrifuge tube fitted with a 24/40 female ground-glass joint, as described in Part I) in 2 ml. of distilled water. Pass tank sulfur dioxide through the suspension until solution is effected and until no test for ferric ion is obtained with thiocyanate.‡

TABLE III.—*Sodium Iron Pyrophosphate Preparation*

A. Analyses of Samples

Source	Run	% Fe*	% P*	Fe/P	% Moisture (2 Hr. at 120 C.)	Drying Procedure
Radioactivity laboratory	1	17.0	22.3	0.76	...	Freeze-drying, followed by pumping at 100 C. to constant weight
	2	15.2	22.7	0.67	...	
	3	14.7	22.7	0.65	...	
	4	14.1	20.9	0.68	9.9	Freeze-drying only
	5	15.8	21.7	0.73	2.2	Same plus pumping 1 hr. at 100 C.
	6	15.0	21.9	0.69	1.9	Freeze-drying only
	7	14.4	20.2	0.71	8.9	Same plus pumping 1 hr. at 100 C.
Commercial product		15.1	....	....	...	Probably dried at 95-100 C.
		14.8†	21.7	0.69	...	
Theoretical $2(Na_4P_2O_7).Fe_4(P_2O_7)_3$		17.5	24.2	0.72	...	

B. Conversion Efficiencies

Sample	Product % Fe	Yield: Mg. Product	Yield: Mg. Fe	Yield: % ‡
1	17.0	98	16.6	110
2	15.2	88	13.4	89
3	14.7	98	14.4	96
4	14.1	99	14.0	93
5	15.8	97	15.3	102
6	15.0	100	15.0	100
7	14.4	101	14.5	97

* Analysis "as is."
† Duplicate analyses.
‡ Based on 15.0 mg. Fe initially.

TABLE IV.—*Iron Powder Preparation*

Run	Product % Fe	Yield: Mg. Product	Yield: Mg. Fe	Yield: % *
1.....	99.5	7.5†	7.5†	50.0†
2.....	98.9	14.8	14.6	97.6
3.....	96.5‡	15.0	14.5	96.5
4.....	98.7	13.9	13.7	91.6

* Based on 15.0 mg. Fe initially.
† Material was lost due to failure to fasten ground glass pieces together firmly with rubber bands or spring binder.
‡ Minimum value due to difficult solubility of this sample in dilute acid used for solution.

‡ It was found that complete reaction could be assured by continuing the sulfur dioxide treatment for two hours. The reduction reactions may be written thus:

$$2\,Fe(OH)_3 + 3\,SO_2 \rightarrow 2\,Fe^{++} + SO_4^{=} + 2HSO_3^{-} + 2\,H_2O.$$

2. Add two drops of concentrated sulfuric acid to convert bisulfite to SO_2.

3. Remove water and excess SO_2 by freeze-drying, as follows. Freeze the solution against the sides of the centrifuge tube by rotating the tube in an acetone-dry ice bath. Attach the tube to male ground-glass joint of a lyophilization apparatus and evacuate. This freeze-drying process takes several hours and is conveniently performed as an overnight operation.

4. Add 5 ml. of acetone to leach out sulfuric acid. Separate the acetone phase from the precipitate of exsiccated ferrous sulfate by centrifugation and decantation.§ Repeat with further 5 ml. portions of acetone ‖ until the wash liquor, when diluted with water, no longer gives a test for sulfate with barium chloride solution.

5. Dry the precipitate to constant weight by evacuation at room temperature.

6. Pulverize the dried powder in the centrifuge tube gently with a spatula.

PART III.—*Preparation of Ferric Orthophosphate from Ferric Hydroxide*

1. The ferric hydroxide is precipitated and washed (as described in Part I) in a 50 ml. centrifuge tube.

2. Dissolve the washed ferric hydroxide in about one-third milliliter of 85% orthophosphoric acid and dilute the solution to 15 ml. with water.

3. Precipitate ferric phosphate by dropwise addition of concentrated ammonium hydroxide until the pH reaches 6.5 (The use of hydrion paper is convenient at this step.)

4. Sedimentate the precipitate by centrifugation, decant the supernatant liquid, and wash by alternate centrifugation and decantation ¶ with four 10 ml. portions of water or a 1 : 1 mixture of ethanol and water.

5. After the final centrifugation and decantation, dry the precipitate in vacuum at about 56 C. (Abderhalden apparatus with boiling acetone).

6. Pulverize the dried precipitate in the centrifuge tube gently with a spatula.

§ It is suggested that this and subsequent wash waters be filtered to recover small amounts of uncentrifuged radioactive iron compounds.

‖ It was found that three washings were required to remove excess acid.

¶ It is suggested that this and subsequent wash waters be filtered to recover small amounts of uncentrifuged radioactive iron compound.

PART IV.—*Preparation of Sodium Iron Pyrophosphate from Ferric Hydroxide*

1. The ferric hydroxide is precipitated and washed in a 50 ml. centrifuge tube fitted with a 24/40 outer ground-glass joint at the top by the method described in Part I.

2. Dissolve the washed ferric hydroxide in 2 ml. (by pipette) of an aqueous solution containing 17.3 ml. concentrated sulfuric acid per liter. Add 2 ml. (by pipette) of an aqueous solution containing 45.0 gm. of $Na_4P_2O_7.10\ H_2O$ per liter. Shake well.

3. Sedimentate the precipitated ferric pyrophosphate by centrifugation and decant the supernatant liquid.# Wash the precipitate free of sulfate ion with three successive 10 ml. portions of distilled water, each followed by centrifugation and decantation.

4. After the final decantation, treat the wet precipitate with 1 ml. (by pipette) of an aqueous solution containing 60.0 gm. $Na_4P_2O_7.10\ H_2O$ per liter. Warm to 55 C. (± 5 C.). Shake the aqueous suspension until any lumps of ferric pyrophosphate are completely dispersed. Standing overnight yields clear solutions.

5. Remove water by freeze-drying, as follows. Freeze the solution against the sides of the centrifuge tube by rotating the tube in an acetone-dry ice bath. Attach the tube to a 24/40 inner joint of a lyophilization apparatus and evacuate. This freeze-drying process takes several hours and is conveniently performed as an overnight operation.

6. Heat in vacuum for two hours at 100 C.

7. Pulverize the dried precipitate with a spatula.

PART V.—*Preparation of Iron Powder from Ferric Hydroxide*

1. The ferric hydroxide is precipitated and washed in a 50 ml. centrifuge tube fitted with a 24/40 outer ground glass joint at the top, as described in Part I.

2. Dry the washed ferric hydroxide by pumping at room temperature for one hour.

3. Cap the centrifuge tube with a 20/40 ground-glass inner joint (Pyrex) * fitted with an inlet (5 mm. inside diameter) and outlet tube and connect the inlet tube to a hydrogen tank. The inlet tube should come to within approximately 1 in. (2.5 cm.) of the bottom of the centrifuge tube. Connect the outlet tube to a water bubbler † with a head of about ½ in. (1.3 cm.).

4. Start the hydrogen gas streaming through the system at a rate of 3 to 4 ml. per minute and flush for about one hour.

5. While maintaining this gas stream, slowly ‡ lower the centrifuge tube into a vertical electric furnace operating at a temperature of 500 C., leaving the ground-glass joint out of the furnace.

6. Maintain these conditions for approximately two hours,§ after which time reduction of hydroxide to metallic iron will be complete.

It is suggested that this and subsequent wash waters be filtered to recover small amounts of uncentrifuged radioactive iron compound.

* Fasten the ground-glass pieces together firmly with rubber bands or a spring binder.

† Interpose a safety catch flask between the bubbler and the centrifuge tube.

‡ The tube must be lowered into the furnace slowly to avoid the loss of powdered iron hydroxide due to the sudden expansion of gas.

§ Actually, reduction is essentially complete within a half hour. We recommend longer exposure to insure the absence of ferric hydroxide.

REFERENCES

1. Nutritionally Improved or Enriched Flour and Bread, Report of the Council on Foods and Nutrition, J. A. M. A. **116**:2849, 1941.

2. Moore, C. V.; Dubach, R.; Minnich, V., and Roberts, H. K.: Absorption of Ferrous and Ferric Radioactive Iron by Human Subjects and by Dogs, J. Clin. Invest. **23**:755, 1944.

3. Hahn, P. F.; Jones, E.; Lowe, R. C.; Meneely, G. R., and Peacock, W.: The Relative Absorption and Utilization of Ferrous and Ferric Iron in Anemia as Determined with the Radioactive Isotope, Am. J. Physiol. **143**:191, 1945.

4. Moore, C. V.; Minnich, V., and Dubach, R.: Absorption and Therapeutic Efficacy of Iron Phytate, J. Am. Dietetic A. **19**:841, 1945.

5. Nakamura, F. I., and Mitchell, H. H.: The Utilization for Hemoglobin Regeneration of the Iron in Salts Used in the Enrichment of Flour and Bread, J. Nutrition **25**:39, 1943.

6. Street, H. R. : A Study of the Availability of the Iron in Enriched Bread, J. Nutrition **26**:187, 1943.

7. Freeman, S., and Burrill, M. W.: Comparative Effectiveness of Various Iron Compounds in Promoting Iron Retention and Hemoglobin Regeneration by Anemic Rats, J. Nutrition **30**:293, 1945.

8. Blumberg, H., and Arnold, A.: The Comparative Biological Availabilities of Ferrous Sulfate Iron and Ferric Orthophosphate Iron in Enriched Bread, J. Nutrition **34**:373, 1947.

9. Conference on Iron Fortification of Foods, the Research Laboratories, Merck & Company, Inc., Rahway, N. J., Aug. 5, 1952.

10. Sterling, K., and Gray, S. J.: Determination of the Circulating Red Cell Volume in Man by Radioactive Chromium, J. Clin. Invest. **29**:1614, 1950.

11. Huff, R. L.; Elmlinger, P. J.; Garcia, J. F.; Oda, J. M.; Cockrell, M. C., and Lawrence, J. H.: Ferrokinetics in Normal Persons and in Patients Having Various Erythropoietic Disorders, J. Clin. Invest. **30**:1512, 1951.

12. Anger, H. O.: Scintillation Counters for Radioactive Sample Measurement, Rev. Scient. Instruments **22**:912, 1951.

13. Dubach, R.; Moore, C. V., and Minnich, V.: Studies in Iron Transportation and Metabolism: V. Utilization of Intravenously Injected Radioactive Iron for Hemoglobin Synthesis and an Evaluation of the Radioactive Iron Method for Studying Iron Absorption, J. Lab. & Clin. Med. **31**:1201, 1946.

14. McCance, R. A.; Edgecombe, C. N., and Widdowson, E. M.: Phytic Acid and Iron Absorption, Lancet **2**:126, 1943.

15. Sharpe, L. M.; Peacock, W. C.; Cooke, R., and Harris, R. S.: The Effect of Phytate and Other Food Factors on Iron Absorption, J. Nutrition **41**:433, 1950.

16. Moore, C. V., and Dubach, R.: Observations on the Absorption of Iron from Foods Tagged with Radioiron, Tr. A. Am. Physicians **64**:245, 1951.

News and Comment

ANNOUNCEMENTS

Symposium on Antimetabolites.—A symposium on the antimetabolites, their modes of action and therapeutic implications, will be held Tuesday, March 1, 1955, at The Biltmore Hotel, New York City.

Morning session—Chairman: Dr. Paul L. Day, University of Arkansas, Little Rock, Ark.

1. Anti-Vitamin E Stress Factors as Related to Fatty Peroxides; E. L. Hove, Alabama Polytechnic Institute, Auburn, Ala.
2. Thiamine Antagonists; L. R. Cerecedo, Fordham University, New York.
3. Vitamin K Antagonists; K. P. Link, University of Wisconsin, Madison, Wis.
4. Folic Acid Antagonists; J. H. Burchenal, Memorial Center for Cancer and Allied Diseases, New York.

Afternoon session—Chairman: Dr. R. W. Heinle, The Upjohn Company, Kalamazoo, Mich.

1. Purine and Pyrimidine Antagonists; G. H. Hitchings, the Wellcome Research Laboratories, Tuckahoe, N. Y.
2. A Naturally Occurring Antimetabolite of Methionine in the Causation of a Disease; D. W. Woolley, The Rockefeller Institute for Medical Research, New York.
3. Pantothenic Acid Antagonists; O. D. Bird, Parke, Davis & Company, Detroit.
4. Vitamin B_6 Antagonists; W. W. Unbreit, Merck Institute for Therapeutic Research, Rahway, N. J.
5. Riboflavin Antagonists; J. P. Lambooy, The University of Rochester, Rochester, N. Y.

Postgraduate Course in Allergy.—A postgraduate course in allergy, on the Modern Management of Allergic Diseases, will be given at The Institute of Allergy of The Roosevelt Hospital, New York, May 9-20, 1955. The fee for the course is $150.00. Enrollment is limited, and those desiring information should write to Dr. Robert A. Cooke, 428 W. 59th St., New York 19.

PARAHEMOPHILIA

CHARLES A. OWEN Jr., M.D.
and
TALBERT COOPER, M.D., Rochester, Minn.

TEN YEARS ago Owren[1] described a patient who had a bleeding diathesis attributable to the lack of a single blood-clotting factor, namely, Factor V, or labile factor.* Owren[8] designated the disease "parahemophilia," to emphasize the clinical similarity to hemophilia. Including the original report, only 45 definite cases, involving 13 families, have been reported (Table 1).

In addition to the definite cases summarized in this table, four presumptive cases have been reported. Rhoads and Fitz-Hugh, in 1941,[19] described a 16-year-old boy whose findings were compatible with a deficiency of the labile factor, although their report was made before the labile factor was recognized. The addition of plasma exposed to adsorption by aluminum hydroxide shortened the patient's "prothrombin time" from 93 seconds to 41 seconds, as compared with a shortening from 93 seconds to 27 seconds by the addition of normal plasma. Cosgriff and Leifer,[20] in 1952, reported on a 66-year-old man; in addition to a deficiency of labile factor, this patient had a reduced concentration of prothrombin and fibrinogen and a reduction in platelets. He was suffering from metastatic prostatic carcinoma. Parahemophilia was diagnosed in a 20-year-old woman by Stohlman and associates,[21] in 1951, because the patient's prolonged "prothrombin time" was shortened by the addition of refined "ac-globulin." This preparation is now known to contain both labile and stable factors.[22] Brennan and associates[23] reported parahemophilia in a 3-year-old boy. The diagnosis was based on an ac-globulin assay value of 6.7%. However, this assay procedure does not necessarily exclude a deficiency of the stable factor. The family histories were negative in three of these cases and not known in the fourth.

Recently we have studied a man who had clinical and laboratory manifestations of this defect; studies also were made of his three children, who presented laboratory evidence of a deficiency of the labile factor but no clinical suggestion of a bleeding tendency.

REPORT OF A CASE

A 47-year-old white man (L) of French-German ancestry was seen at the Mayo Clinic in September, 1952, because of an increasingly severe bleeding tendency.

The family history revealed only one instance of abnormal bleeding; his maternal grandmother had died of postpartum hemorrhage. His father had died at the age of 63 of coronary heart disease; the mother, aged 66, was living but had been bedfast for three years. His three children were healthy; they included a son (F) aged 21, a son (J) 19, and a daughter (Ju) 12.

The patient's history of bleeding diathesis may have dated back to the age of 10 or 12, when, after tonsillectomy, he had experienced a brief but severe hemorrhage. At the age of 30 he had received a blow to the scrotum with subsequent development of a hematoma in the left testicle; orchidectomy was required. In January, 1952, three teeth had been extracted; this was followed by more or less continuous bleeding for six days. The family physician found the clotting time to be 13 minutes and the bleeding time 15 minutes. He prescribed two injections of an analogue of vitamin K, with oral administration of ascorbic acid. Coincidentally or not, the oral bleeding soon subsided, but the laboratory findings were unaltered; the family physician

The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

From the Section of Clinical Pathology (Dr. Owen) and the Section of Medicine (Dr. Cooper), Mayo Clinic and Mayo Foundation.

*Factor V (five) and labile factor are the names proposed by Owren[2] and Quick,[3] respectively. Synonyms include pro-prothrombinase,[2] proaccelerin,[4] ac-globulin (AcG),[5] accelerator,[6] and plasmatic cofactor of thromboplastin.[7]

found the clotting time still lengthened (15 minutes), along with a prolonged "prothrombin time"; platelets were numerically normal.

General examination at the clinic revealed no significant abnormalities except for a small epithelioma on the right shoulder. This tumor was fulgurated, and healing occurred without complication.

Hematologic studies disclosed the following values: hemoglobin, 14.5 gm. per 100 ml.; erythrocytes and leucocytes numbered 4,460,000 and 7,000 per cubic millimeter, respectively; the platelet count was 199,000 per cubic millimeter; bleeding time was five minutes; the clotting time of whole blood, determined on several occasions in plain dry tubes at room temperature, ranged from 7½ to 12 minutes; "prothrombin times" varied from 37 to 40 seconds (18 seconds for normal plasma). The erythrocytic sedimentation rate was 30 mm. during the first hour (Westergren method). The value for serum bilirubin was 0 (direct) and 0.7 mg. per 100 ml. (indirect). Blood urea measured 36 mg. Results of the Kline flocculation test for syphilis were negative. There was no sulfobromophthalein evident in the blood 60 minutes after the intravenous injection of 5 mg. of the dye per kilogram of body weight. Urinalysis disclosed nothing remarkable. Roentgenographic studies of the thorax, gall bladder, kidney-ureter-bladder system, stomach, and duodenal cap revealed no abnormalities. Electrocardiographic tracings were interpreted as being virtually normal.

LABORATORY INVESTIGATION

Because of the abnormal "prothrombin times" without any evidence of the usual causes (disease of the liver or biliary tract, deficiency of vitamin K, consumption of bishydroxycoumarin (Dicumarol) or related drugs), further studies with regard to coagulation were undertaken.

Just as in Owren's patient, our patient was found to have a normal concentration of prothrombin by a modification [24] of the two-stage test of Warner, Brinkhous, and Smith. However, the speed with which thrombin could form from the available plasma prothrombin was retarded to 8% of the normal rate under standardized conditions.

Retarded conversion of prothrombin, which is a characteristic of deficiency in labile factor, is no longer enough to justify the diagnosis of parahemophilia, for another clotting factor has been found to have the same property. Shortly after the reports of Owren, several publications † appeared from the Mayo Clinic indicating that a second factor existed and that it was also important in

TABLE 1.—*Reported Definite Cases of Parahemophilia*

	Symptomatic Parahemophiliacs					Asymptomatic Parahemophiliacs		
Authors	Case	Age, Yr.	Sex	Relationship	Familial History	Number of Persons	Sex	Relationship
Owren [1, 2] (1944 and 1947)	1	29	F	.....	Neg.	..	..	.....
Hauser [9] (1950)	2	?	M	Sibs	Pos.	..	..	.....
	3	?	M					
Frank, Bilhan, & Ekren [10] (1950)	4	29	M	.....	Pos.	..	..	.....
Marx [11] (1950)	5	24	F	.....	Neg.	..	..	.....
de Vries, Matoth, & Shamir [12] (1951)	6	15	F	Sibs	Pos.	..	..	.....
	7	11	M					
	8	6	F					
Alexander & Goldstein [13] (1952)	9	17	F	.....	Neg.	1	M	Sibs of Case 9
						1	F	
Brink & Kingsley [14] (1952)	10	32	F	Sibs	Pos.	9	F	Relatives of 10, 11, & 12 through 4 generations
	11	27	F			10	M	
Kingsley [15] (1954)	12	13	M			1	M	Apparently unrelated to others
Owren [16] (1953)	13	5	M	.....	Neg.	1	F	Mother of Case 13
						1	M	Sib of Case 13
Redner, Scalletar, & Weiner [17] (1953)	14	5	F	.....	?	..	..	.....
Kingsley [18] (1954)	15	8	M	Sibs	Pos.	2	M	Father & sib of Cases 15 and 16
	16	7	F			1	F	Mother of Cases 15 and 16
Heni & Krauss [18] (1954)	17	1	M	.....	Pos.	..	..	.....
	18	8	M	.....	Pos.			
Owen & Cooper (present study)	19	47	M	.....	Neg.	2	M	Children of Case 19
						1	F	

† References 25-29.

TABLE 2.—*Demonstration of Deficiency of Labile Factor in Plasma of Patient L*

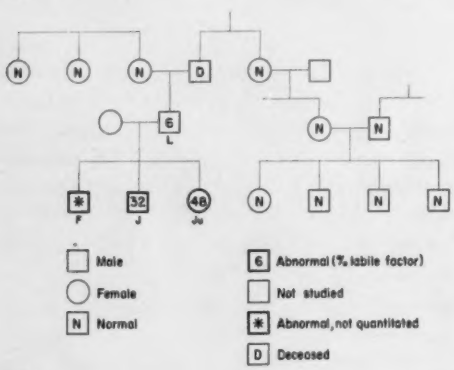
	"Prothrombin Time," Sec.
Normal human plasma (oxalated)	17
L's plasma (oxalated)	34
Stored human plasma (oxalated)	110
$Ca_3(PO_4)_2$-adsorbed plasma (oxalated)	Incoagulable
Human bishydroxycoumarin plasma (oxalated)	83
Stored plasma 9 parts	
+ 1 part normal plasma	29
+ 1 part L's plasma	81*
Adsorbed plasma 9 parts	
+ 1 part normal plasma	32
+ 1 part L's plasma	31
Bishydroxycoumarin plasma 9 parts	
+ 1 part normal plasma	29
+ 1 part L's plasma	29
L's plasma 9 parts	
+ 1 part normal plasma	28
+ 1 part bishydroxycoumarin plasma	28

* L's plasma barely shortened the "prothrombin time" of the stored plasma, which was practically free of the labile factor.

the early phases of coagulation; this was a stable factor [30] with cothromboplastic activity.[31]‡ It is apparent that patients previously described as having "idiopathic hypoprothrombinemia" may well have lacked the labile factor; the stable factor, as in the case of

‡ The concept of a stable factor has been repeatedly confirmed; however, other designations have been used, such as serum prothrombin conversion accelerator,[32] proconvertin,[33] and Factor VII.[34]

Fig. 1.—Schematic representation of the findings in a study of the family of a parahemophiliac (L). The symbols are explained in the lower part of the figure.



Frick and Hagen,[35] or both factors, as described by Crockett and co-workers.[36]

Table 2 summarizes the evidence that the deficiency in our patient (L) is of the labile factor and not of the stable factor. The "prothrombin time" of his oxalated plasma was corrected to the same extent by normal plasma or by plasmas deficient in the stable factor, which was eradicated completely by adsorption with calcium phosphate or partially by the administration of bishydroxycoumarin to patients whose plasmas then were used in this study. These corrective plasmas all contained a normal concentration of labile factor. Contrastingly, the patient's abnormal "prothrombin time" was reduced only slightly by the addition of normal plasma that had been stored at 5 C. until its content

TABLE 3.—*Titration of Labile Factor in Plasma*

	Average "Prothrombin Time," Sec.
A. Test plasmas, source *	
Normal (human)	18
Stored (human)	138
L	35
J	22
Ju	20

B. Standardization		"Prothrombin Time," Sec.	Final Concentration of Labile Factor, %
Normal plasma 1 part			
+ stored plasma	9 parts	27	10.0
	19 parts	33	5.0
	39 parts	41	2.5
	79 parts	54	1.25
	159 parts	69	0.63
	319 parts	85	0.31

C. Titration	"Prothrombin Time," Sec.	% Concentration of Labile Factor in Diluted Plasma, Equivalent to Control †	Labile Factor in Original Plasma, % ‡
Stored plasma 9 parts			
+ 1 part normal plasma	27	10.0	100
+ 1 part L's plasma	94	0.3	3
+ 1 part J's plasma	41	2.5	25
+ 1 part Ju's plasma	35	5.0	50

* All these plasmas were oxalated.
† From the standardization (*B*).
‡ Corrected for the 10-fold dilution of the test plasma.

of labile factor was extremely low, its concentration of stable factor remaining practically normal.

Despite the absence of histories of abnormal bleeding among living members of the family, it was decided to study two available branches (Fig. 1). It was found that two of our patient's children (J and Ju) had distinct but lesser deficiencies of the labile factor. Another brother (F) was studied on several occasions at the Oscar B. Hunter Memorial Laboratory, in Washington, D. C.§; in every instance his "prothrombin time" was slightly lengthened to an average of 18 seconds, compared with control values of 15 seconds. In the absence of more specific data it can only be assumed that the plasma of F was deficient in the labile factor; as judged by the "prothrombin times," it probably was deficient to about the same extent as it was in siblings J and Ju.

Table 3 demonstrates our routine method for evaluation of the labile factor. Table 4 summarizes the results of this and other methods for estimation of the concentration of the labile factor. An average of the results of the various methods indicates a calculated concentration of labile factor, expressed as per cent of normal, of 6 for L, the father; 32 for the son, J, and 48 for the daughter, Ju. Lack of bleeding tendencies in these children suggests that actual bleeding occurs only when the level of the labile factor is extremely low.

§ Dr. Oscar B. Hunter, Jr., aided in this study.

TABLE 4.—*Summary of Assays of Labile Factor*

Plasma	Average "Prothrombin Time," Sec.*	"Prothrombin Activity," % †	Assay of Labile Factor, %			Average of Assays
			With Normal Plasma ‡	With Adsorbed Plasma §	Convertibility ‖	
L	34	20	3	6	8	6
J	22	50	25	30	40	32
Ju	20	65	50	45	50	48
Normal	17-18	100	100	100	100	100

* Mayo Clinic adaptation of the Quick test.[37]
† Based on a curve derived from the "prothrombin times" of normal plasma diluted with isotonic sodium chloride solution.
‡ Detailed in Table 3.
§ Adsorbed plasma ($Ca_3[PO_4]_2$) was used instead of whole normal plasma to establish the standard curve with stored plasma.
‖ Under standardized conditions, the rate of formation [24] of thrombin was measured by means of the two-stage test. The actual prothrombin titers were L, 91%; J, 94%, and Ju, 101% of three normal plasmas that averaged 356 units of prothrombin per milliliter.

COMMENT

Parahemophilia, despite its apparent rarity, is of interest from both laboratory and clinical standpoints. The diagnosis rests on laboratory study; knowledge of the genetic future of the patient, as well as the immediate treatment, depends on precise diagnosis.

The differential diagnosis of parahemophilia is basically the distinction between a lengthened "prothrombin time" caused by lack of labile factor and prolonged "prothrombin times" from other causes. This distinction may be clarified by an outline of the basic steps in clotting: 1. Plasma thromboplastins ‖ are apparently activated by platelets; a lack of the former is related to hemophilia, whereas lack of the latter is related to thrombocytopenia. 2. The activated thromboplastin forms complexes with the labile and stable factors. 3. The thromboplastin complex, in the presence of calcium, converts prothrombin into thrombin. 4. Thrombin enzymically converts fibrinogen into fibrin.

Steps 3 and 4 are essentially the same as those proposed by Morawitz, in 1905.[41] Hints of Step 2 might be interpreted from the early work of Nolf [42] and that of Bordet

‖ These include such components as antihemophilic globulin, which is believed by some workers to be lacking in hemophilia; plasma thromboplastin component (PTC or PTF-B),[38] which is deficient in a hemophilia-like disease known in Great Britain as "Christmas disease," [39] and plasma thromboplastin antecedent (PTA).[40]

and Gengou, as reflected in their paper written in 1904;[43] however, present concepts of the mechanism of the thromboplastin complex can be attributed to Mann and Hurn[31] and to Flynn and Coon.[44] From these later reports it is evident that the labile and stable factors hold a unique place in clotting. A reduction or absence of either factor leads to a prolonged "prothrombin time," for the addition of any amount of extract of brain (thromboplastin) cannot overcome their deficiency. On the other hand, the hemophilic group of diseases is characterized by lack of certain thromboplastic elements, which lack is masked in vitro by the addition of tissue thromboplastin, resulting in a normal "prothrombin time" as the test is usually done.

Thus, the Quick test of "prothrombin time" can distinguish the hemophilic group

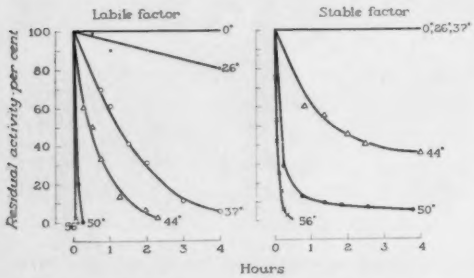


Fig. 2.—Comparison of residual activity of stable factor and labile factor in oxalated specimens of normal human plasma at various temperatures.

of diseases from those resulting from lack of the labile and stable factors. To determine which of the latter is responsible for a bleeding tendency is of more than academic interest; it is of diagnostic and therapeutic importance. An isolated deficiency of the labile factor (parahemophilia) demands fresh blood or plasma for effective treatment, because of the instability of the labile factor (Fig. 2). In the treatment of an isolated deficiency of the stable factor no special precaution for the preservation of blood for transfusion is required. Most important is the recognition of the commoner multiple deficiencies that also may prolong the "prothrombin time," for treatment depends on recognition of the cause. Such factors include deficiency of prothrombin and stable factor in deficiency of vitamin K, deficiency primarily of stable factor and secondarily of prothrombin associated with use of bishydroxycoumarin, deficiency of labile and stable factors as well as of prothrombin in certain hepatic injuries, and primary reduction of prothrombin in chronic hepatic disease. If the "prothrombin time" alone were used, differentiation of these various potential bleeding states would be difficult.

Since relatively simple techniques are now available to distinguish the labile factor from the stable factor, it appears likely that more cases of parahemophilia will be recognized. Despite the limited number of cases reported, it is clear that the disease affects both sexes. In six families it has been found in two or more siblings. In only four unrelated families, including the one featured in this report, has laboratory confirmation of the disease been found in more than one generation of any single family.

In the family studied by Brink and Kingsley[14] and by Kingsley,[15] both parents had normal "prothrombin times" but reduced concentrations of labile factor in the plasma. All nine of their children were studied; three had definite parahemophilia with bleeding; four had diminished labile factor but no bleeding, and the other two were normal. Five of the 15 grandchildren had deficiencies in labile factor; only one of the remaining 10 was an offspring of an abnormal parent. Brink and Kingsley pointed out that the inheritance could be explained by a recessive gene or by a dominant gene with incomplete penetrance. If the gene for parahemophilia were a recessive, then both parents would be required to have the tainted gene in order to transmit the disease in recognizable form; this appears a little unlikely in this particular family, in which a history of bleeding was obtained through four generations.

The genetic alternative is to suggest an incompletely dominant gene, which does not require that both parents be affected; this also would account for the variable intensity of the disease in succeeding generations. If

a parahemophilic person were homozygous (PP) or heterozygous (Pp), where P is the abnormal dominant and p the normal recessive, the offspring of mating between a parahemophiliac and a normal spouse would be either (1) PP × pp = all Pp (all parahemophiliacs) or (2) Pp × pp = 1 Pp : 1 pp (half the offspring parahemophilic and half normal).

Kingsley [15] recently has suggested that the plasma of a homozygous parahemophiliac is almost entirely lacking in labile factor and that thus he is a bleeder; the heterozygous person has only a partial deficiency and is usually not a bleeder.

The concept of a dominant gene for parahemophilia could explain the family reported by de Vries and associates,[12] in which the "prothrombin time" of the father was normal, that of the mother slightly prolonged, and that of all three children significantly lengthened. The family in our report is much like that of de Vries and co-workers, except that in ours the only clinical bleeding was in the father, with all three children having much milder deficiencies in labile factor. In the extensive genetic study by Kingsley of one family, 38 children were studied; the parahemophilic tendency was found in 18, which approaches the 1 : 1 ratio to be expected in Pp × pp matings. Syndactyly, found along with parahemophilia together and separately in the family reported by de Vries and co-workers, appears coincidental, as no other family with the same defect has been reported.

Summarizing the limited literature and current report from a clinical viewpoint, one finds parahemophilia in either sex and at all ages. It is clearly a familial disease. A total of 8 parahemophiliacs with 23 affected children or grandchildren have been reported; only 6 of the offspring had bleeding tendencies. The disease may be more severe in the parent or in the children and may be of variable severity among siblings. In one patient studied for many months by Brink and Kingsley, the "prothrombin time" fluctuated between 37 and 70 seconds and tended to remain at certain levels for several weeks. Thus, the finding of a minimal deficiency of the labile factor on one occasion is apparently no sign that the level will remain constant. However, our patient, L, when restudied three months after his first examination, had a concentration of labile factor almost identical with that found initially.

The only treatment of known value is transfusion with fresh blood or plasma; the deficiency of labile factor may be corrected to a clinically significant degree for a day or so [14] after each transfusion. Administration of vitamin K has been uniformly unsuccessful.

SUMMARY

A father and his three children were found to have a defect in the mechanism for coagulation of blood known as parahemophilia, or Owren's disease, which is characterized by a deficiency of the labile factor. The deficiency was severe enough in only the father to cause bleeding. In agreement with published reports, both sexes in this family were involved and the inheritance was direct from one generation to the next, perhaps as the result of an incompletely dominant gene. Studies of 10 other relatives revealed no further instances of the disease.

The place of the labile factor and its closely related stable counterpart in the coagulation of blood is discussed. A deficiency of either factor is reflected in prolonged "prothrombin times" as determined by the Quick test, a situation unlike that in hemophilia, with its normal "prothrombin time."

Treatment for the bleeding of parahemophilia consists of transfusions of fresh blood or plasma that, because of its freshness, is rich in labile factor.

REFERENCES

1. Owren, P.: Nye undersøkelser over blodets koagulasjon, Det Norske Videnskaps-Akademi i Oslo, pp. 21-22 (Nov.) 1944.

2. Owren, P. A.: The Coagulation of Blood: Investigations on a New Clotting Factor, Acta med. scandinav., Supp. 194, pp. 1-327, 1947.

3. Quick, A. J.: Congenital Hypoprothrombinaemia and Pseudohypoprothrombinaemia, Lancet **2**:379-382 (Sept. 13) 1947.

4. Astrup, T.: Blood Clotting and Related Processes, in Nord, F. F.: Advances in Enzymology and Related Subjects of Biochemistry, New York, Interscience Publishers, Inc., 1950, Vol. 10, pp. 1-49.

5. Ware, A. G.; Guest, M. M., and Seegers, W. H.: Plasma Accelerator Factor and Purified Prothrombin Activation, Science **106**:41-42 (July 11) 1947.

6. Fantl, P., and Nance, M.: Acceleration of Thrombin Formation by a Plasma Component, Nature, London **158**:708-709 (Nov. 16) 1946.

7. Honorato, R.: The Plasmatic Cofactor of Thromboplastin: Its Adsorption, with Prothrombin and Fibrinogen, by Alumina and Tricalcium Phosphate Gels, Am. J. Physiol. **150**:381-388 (Sept.) 1947.

8. Owren, P. A.: Parahaemophilia: Haemorrhagic Diathesis Due to Absence of a Previously Unknown Clotting Factor, Lancet **1**:446-448 (April 5) 1947.

9. Hauser, F.: Idiopathische Hypoprothrombinämie versus Mangel an Faktor V, Ann. pædiat. **174**:19-28, 1950.

10. Frank, E.; Bilhan, N., and Ekren, H.: Die Parahämophilie (Owren), eine neue Form der hämorrhagischen Diathese, Acta haemat. **3**:70-90 (Feb.) 1950.

11. Marx, R.: Konstitutionelle Pseudohypoprothrombinaemien, Ärztl. Forsch. **4**:567-576 (Oct. 25) 1950.

12. de Vries, A.; Matoth, Y., and Shamir, Z.: Familial Congenital Labile Factor Deficiency with Syndactylism: Investigation on the Mode of Action of the Labile Factor, Acta haemat. **5**:129-142 (March) 1951.

13. Alexander, B., and Goldstein, R.: Parahemophilia in 3 Siblings (Owren's Disease); With Studies on Certain Plasma Components Affecting Prothrombin Conversion, Am. J. Med. **13**:255-272 (Sept.) 1952.

14. Brink, A. J., and Kingsley, C. S.: A Familial Disorder of Blood Coagulation Due to Deficiency of the Labile Factor, Quart. J. Med. **21**:19-31 (Jan.) 1952.

15. Kingsley, C. S.: Familial Factor V Deficiency: The Pattern of Heredity, Quart. J. Med. **23**:323-329 (July) 1954.

16. Owren, P. A.: Prothrombin and Accessory Factors: Clinical Significance, Am. J. Med. **14**:201-215 (Feb.) 1953.

17. Redner, B.; Scalettar, H., and Weiner, M.: Parahemophilia (Owren's Disease), Pediatrics **12**:5-10 (July) 1953.

18. Heni, F., and Krauss, I.: Angeborener Faktor V-Mangel (Owrensche Krankheit), Klin. Wchnschr. **32**:633-635 (July 15) 1954.

19. Rhoads, J. E., and Fitz-Hugh, T., Jr.: Idiopathic Hypoprothrombinemia—an Apparently Unrecorded Condition, Am. J. M. Sc. **202**:662-670 (Nov.) 1941.

20. Cosgriff, S. W., and Leifer, E.: Factor 5 Deficiency in Hemorrhagic Diathesis (Parahemophilia), J. A. M. A. **148**:462-463 (Feb. 9) 1952.

21. Stohlman, F.; Harrington, W. J., and Moloney, W. C.: Parahemophilia (Owren's Disease): Report of a Case in a Woman with Studies on Other Members of Her Family, J. Lab. & Clin. Med. **38**:842-845 (Dec.) 1951.

22. Alexander, B.; Goldstein, R., and Landwehr, G.: The Prothrombin Conversion Accelerator of Serum (SPCA): Its Partial Purification and Its Properties Compared with Serum Ac-Globulin, J. Clin. Invest. **29**:881-895 (July) 1950.

23. Brennan, M. J.; Monto, R. W., and Shafer, H. C.: Hemorrhagic Diathesis Due to Ac-Globulin Deficiency, Am. J. Clin. Path. **22**:150-154 (Feb.) 1952.

24. Owen, C. A., Jr.; Magath, T. B., and Bollman, J. L.: Prothrombin Conversion Factors in Blood Coagulation, Am. J. Physiol. **166**:1-11 (July) 1951.

25. Owen, C. A.: Experimental Alteration of the Rate of Thrombin Formation During Blood Clotting, Bull. Am. Coll. Surgeons **32**:256 (Sept.) 1947.

26. Mann, F. D.; Hurn, M., and Magath, T. B.: Observations on the Conversion of Prothrombin to Thrombin. Proc. Soc. Exper. Biol. & Med. **66**: 33-35 (Oct.) 1947.

27. Owen, C. A., and Bollman, J. L.: Prothrombin Conversion Factor of Dicumarol Plasma, Proc. Soc. Exper. Biol. & Med. **67**:231-234 (Feb.) 1948.

28. Mann, F. D.: Co-Thromboplastin Assay: A Means of Study of Abnormalities of Blood Coagulation, Am. J. Clin. Path. **19**:861-864 (Sept.) 1949.

29. Owen, C. A., Jr.: Studies on the Conversion of Prothrombin to Thrombin: Effect of Conversion Variations on Prothrombin Tests, Thesis, University of Minnesota, 1950.

30. Owen, C. A., Jr., and Bollman, J. L.: Analysis of the One-Stage Test for Prothrombin Time, J. Appl. Physiol. **5**:515-525 (March) 1953.

31. Mann, F. D., and Hurn, M.: Co-Thromboplastin, a Probable Factor in Coagulation of Blood, Am. J. Physiol. **164**:105-110 (Jan.) 1951.

32. Alexander, B.; de Vries, A.; Goldstein, R., and Landwehr, G.: A Prothrombin Conversion Accelerator in Serum, Science **109**:545 (May 27) 1949.

33. Owren, P. A., and Bjerkelund, C.: A New, Previously Unknown Clotting Factor, Scandinav. J. Clin. & Lab. Invest. **1**:162-163, 1949.

34. Koller, F.; Loeliger, A., and Duckert, F.: Experiments on a New Clotting Factor (Factor VII), Acta haemat. **6**:1-18 (July) 1951.

35. Frick, P. G., and Hagen, P. S.: Congenital Familial Deficiency of the Stable Prothrombin Conversion Factor: Restudy of Case Originally Reported as "Idiopathic Hypoprothrombinemia," J. Lab. & Clin. Med. **42**:212-223 (Aug.) 1953.

36. Crockett, C. L., Jr.; Shotton, D.; Craddock, C. G., Jr., and Leavell, B. S.: Hypoprothrombinemia: Studies of a Case of the Idiopathic Type and the Effect of Serum Administration, Blood **4**:1298-1309 (Dec.) 1949.

37. Hurn, M.; Barker, N. W., and Magath, T. B.: The Determination of Prothrombin Time Following the Administration of Dicumarol, 3,3'-Methylenebis(4-Hydroxycoumarin), with Special Reference to Thromboplastin, J. Lab. & Clin. Med. **30**:432-447 (May) 1945.

38. Aggeler, P. M.; White, S. G.; Glendening, M. B.; Page, E. W.; Leake, T. B., and Bates, G.: Plasma Thromboplastin Component (PTC) Deficiency: A New Disease Resembling Hemophilia, Proc. Soc. Exper. Biol. & Med. **79**:692-694 (April) 1952.

39. Biggs, R.; Douglas, A. S.; MacFarlane, R. G.; Dacie, J. V.; Pitney, W. R.; Merskey, C., and O'Brien, J. R.: Christmas Disease: A Condition Previously Mistaken for Haemophilia, Brit. M. J. **2**:1378-1382 (Dec. 27) 1952.

40. Rosenthal, R. L.; Dreskin, O. H., and Rosenthal, N.: New Hemophilia-like Disease Caused by Deficiency of a Third Plasma Thromboplastin Factor, Proc. Soc. Exper. Biol. & Med. **82**:171-174 (Jan.) 1953.

41. Morawitz, P.: Die Chemie der Blutgerinnung, Ergebn. Physiol. **4**:307-422, 1905.

42. Nolf, P.: The Coagulation of the Blood, Medicine **17**:381-411 (Dec.) 1938.

43. Bordet, J., and Gengou, O: Recherches sur la coagulation du sang: (Quartrième mémoire) Sur le pouvoir coagulant du serum, Ann. inst. Pasteur **18**:98-115 (Feb.) 1904.

44. Flynn, J. E., and Coon, R. W.: Purification and Isolation of Certain Intermediates Formed Prior to the Activation of Prothrombin, Am. J. Physiol. **175**:289-295 (Nov.) 1953.

CHLORPROMAZINE AS A THERAPEUTIC AGENT IN CLINICAL MEDICINE

JOHN H. MOYER, M.D.
VERNON KINROSS-WRIGHT, M.D
and
R. MILTON FINNEY, M.D., Houston, Texas

CHLORPROMAZINE (10-[γ-dimethylaminopropyl] - 2 - chlorophenothiazine hydrochloride) is a phenothiazine derivative which has been reported to be effective in the treatment of a wide variety of clinical conditions.* Preliminary observations have indicated that it is useful in neuroses and psychoses,† nausea and vomiting,‡ shock,[11] and as an agent to augment the effect of anesthetics and opiates.[12] The purpose of the present report is to present a summary of results obtained when chlorpromazine was used for the treatment of neuropsychiatric disorders, for nausea and vomiting of diverse causation, and for intractable hiccoughs. In these studies each patient served as his own control.

The results reported for the neuropsychiatric patients should be considered qualitative rather than quantitative observations. The primary purpose of this aspect of the study was an attempt to estimate therapeutic applicability in varied neuropsychiatric disorders. In addition, attempts were made to establish the maximum, as well as the most satisfactory, dosage schedules.

METHODS AND MATERIALS

Treatment of Neuropsychiatric Disorders

Patients and Dosage Schedule.—Four hundred twelve unselected patients covering a wide range of neuropsychiatric disorders were observed. The duration of illness varied greatly. Many of the patients were suffering their first attack; others had had repeated attacks and had spent long periods in mental hospitals. A majority had been treated by other methods, including sedation, psychotherapy, and prefrontal lobotomy, without lasting benefit. A few of the patients in this series were given other treatments in addition to chlorpromazine. Of this number only those patients are included in whom chlorpromazine played a major role in the therapeutic result. It is recognized that the outcome of any one psychiatric treatment depends upon many months or even years of observation. However, these patients have been followed (and treated) for as long as one year.

For purposes of analysis the patients have been divided into two groups. Those in Group I were patients with neuroses and other minor mental and emotional disorders. Those in Group II were mostly psychotics, many of whom were acutely disturbed and had been placed in the hospital involuntarily. Patients in Group I were ambulatory, while those in Group II were hospitalized.

The majority of the ambulatory patients were given 5 to 50 mg. of chlorpromazine three to four times daily by mouth. Postprandial administration was preferred, because of complaints of heartburn and occasional nausea when the drug was given on an empty stomach. A few of the ambulatory patients were given as much as 800 mg. daily by mouth.

For initial treatment of hospitalized patients the intramuscular route of drug administration was found to be preferable. Characteristically, therapy in the psychotic patient was initiated with 50 mg. intramuscularly given every four to six hours. After 24 hours the dose was doubled. By the third or fourth day the route of drug administration was gradually changed from the intramuscular to the oral one and the dose was increased daily by 200 mg. until improvement in the basic illness was observed. The usual maximum dose per patient ranged between 1,000 and 1,600 mg. per day. As much as 4,000 mg. was given to one patient over a 24-hour period. While it was sometimes necessary to use more than 3,000 mg. per day, when this was done there was a marked increase in severity of the complications, especially the Parkinsonian syndrome. The maximum dose was continued for a week to 10 days and then, depending upon an improved clinical course, gradually reduced to a maintenance level, usually a fraction of the maximum

From Departments of Medicine, Psychiatry, and Pharmacology, Baylor University College of Medicine.

In the United States chlorpromazine was first designated as SKF #2601-A and is now called Thorazine; in Canada, England, France, and Italy it is called Largactil; in Germany, Megaphen, and in Argentina, Ampliactil.

* References 1-12.

† References 1-6.

‡ References 7-10.

dose. The length of time for which the patient took the maintenance dose varied. Some were able to stop it in a few weeks without return of symptoms; others relapsed promptly if the drug was reduced or withdrawn.

Gradation of Results.—The therapeutic efficacy, side-reactions, complications, and amount and duration of treatment have been recorded. Clinical results in the ambulatory patients, Group I, were graded as follows: Excellent, for those patients who experienced total remission or relief of symptoms interfering with normal life, work, and social activities; good, for those whose general symptoms were improved or whose presenting symptom was removed; poor, for those who obtained only transient, slight, or no relief.

A slightly different system was used for judging the results in the hospitalized patients, Group II. Remission implies disappearance of subjective and objective evidence of mental disease, with resumption of normal life. Much improved refers to patients able to live at home and even work but who still have residual symptoms and/or signs. Improved signifies those patients who were relieved of incapacitating elements but whose basic illness persisted in modified form. Failure indicates no change in status. In addition to clinical evaluation a number of the patients were followed with serial biochemical and psychological studies.

Side-reactions to chlorpromazine were graded from 1 to 3 in increasing order of severity, as were the complications. The hospitalized patients had vital signs recorded four times daily.

Treatment of Nausea and Vomiting

Dosage.—Adult patients were given 10 mg., 25 mg., or 50 mg. doses by either the oral or the intramuscular route, repeated at varying intervals as needed to control symptoms. In many instances it was found that initially the patients were, because of vomiting, unable to retain the capsules by mouth for a long enough period of time to obtain adequate absorption of the drug. Therefore, the first dose was usually given intramuscularly or rectally. After vomiting was under control, the drug was administered by the oral route. Those cases reported as having received the drug by the intramuscular route are patients in whom the drug was never administered orally. Contrariwise, many of the patients who were recorded as having received the drug orally were given the initial dose intramuscularly or rectally (suppository), but after their vomiting was arrested they were maintained on the drug by the oral route.

Gradation of Results.—The responses to chlorpromazine were studied to determine the therapeutic efficacy, the side-reactions, and the duration of action. Therapeutic efficacy was judged as excellent in those cases in whom vomiting stopped and the nausea was completely relieved, good when vomiting stopped although slight nausea persisted, fair when vomiting stopped but nausea continued, and failure in those cases unrelieved by chlorpromazine. Nausea and vomiting were controlled in many of the patients after several doses of the drug. Placebos were substituted whenever there was a question of psychic versus drug effect. Placebos which appeared exactly like the chlorpromazine medication (capsules for those on oral therapy, saline injections for those on parenteral therapy) were substituted periodically to test for continued drug response in patients who received the drug for prolonged periods. Prior to and at frequent intervals after the administration of chlorpromazine the patient's pulse rate and blood pressure were recorded. In addition, the patient was also observed for evidence of sedation, dizziness, dryness of the mouth, and other side-reactions, which were graded from 1 to 4 according to their severity.

Table 1.—*Summary of Results with Chlorpromazine in Psychiatry Office Patients (Group I)*

Diagnosis	Patients, No.	Therapeutic Results		
		Excellent	Good	Poor
Tension state	109	78	24	7
Anxiety neurosis	31	22	6	3
Depression, reactive	38	18	13	7
Ambulatory schizophrenia	13	2	11	0
Conversion hysteria	2	0	0	2
Migraine	3	2	1	0
Epilepsy	6	4	2	0
Confusion, with cerebral disease	2	1	0	1
Postalcoholic state	3	0	2	1
Narcotic addiction	1	1	0	0
Senile depression	1	1	0	0
Behavior disorders in children	8	6	2	0
Total	217	135	61	21

RESULTS

Treatment of Neuropsychiatric Disorders

Ambulatory Patients.—Table 1 summarizes our results in this group, which includes patients with tension states, anxiety neuroses, reactive depressions, and ambulatory schizophrenia.

The diagnosis of tension state describes patients who presented one or more features of tension as their chief complaint. Nervousness, irritability, fatigue, headache, muscular aches and cramps, and inability to concentrate were common symptoms. In addition, anorexia, obesity, dysmenorrhea, diarrhea, indigestion, and insomnia were mentioned by many. Almost all of the patients had been treated in other ways. Psychotherapy, sedation, stimulants, and hormone therapy had been used, with varying degrees of relief. Patients who were judged to have obtained an excellent therapeutic result without exception felt better on chlorpromazine than on any other regimen. With some, relief was immediate; others required manipulation of dosage for best effect. Contrary to expectation, it was found that these patients often obtained more benefit from small rather than large doses. With doses of 50 mg. or more, taken three times a day, these patients were frequently so bothered by the side-effects of medication that they became disheartened. By contrast, the side-effects were minimal when doses of 15 to 30 mg. daily were used. In more acute tension states medication has been discontinued after a few weeks, with persistence of benefit. Many patients were on a regular schedule at first but later took chlorpromazine only as needed to meet emergency situations that increased their state of tension. Failures in this group occurred mainly in patients with fixed somatic complaints and immature personalities.

Typical anxiety neuroses were encountered in 31 persons. They responded in much the same way as did the patients with tension states; that is, about two-thirds obtained an excellent response. Poor results or failures appeared to be associated with extreme chronicity and fixed somatization reactions. However, one 59-year-old man with intractable psychogenic neck pain who had required opiates for eight years became free from pain in one week, though other anxiety symptoms persisted. Improved sleeping, increased appetite, and reduction of nervousness were the first signs that a good response could be expected.

The mild to moderately severe depressive reactions included in this group occurred in response to adverse environmental happenings, sometimes associated with physical suffering or handicap. Others could be regarded as menopausal in origin, while some occurred against a background of longstanding neurotic tendencies. Relief of depression and its associated symptoms occurred in 18 of 38 patients. Thirteen others, whose response was graded good, felt considerably better, gained weight, slept, and took more interest in their affairs. The seven patients who obtained a poor result either failed to respond or were obliged to discontinue the drug because of side-effects.

Thirteen schizophrenics were treated, most of whom were chronic cases leading a secluded life outside of the hospital. All experienced marked relief from annoying symptoms, particularly those associated with tension, but promptly relapsed if they discontinued the drug. Two of this group who had acute schizophrenia of a few days' duration, exhibiting bizarre behavior with florid delusions and hallucinations, responded so well that their hospitalization became unnecessary. Within a month symptoms of the illness in both patients were absent.

Patients with chronic conversion hysteria of the paralytic variety failed to show a favorable response to small doses of chlorpromazine.

Migraine attacks were alleviated considerably. Of the three migraine sufferers treated, two have obtained more relief and have had fewer attacks when taking small doses of chlorpromazine, along with salicylates, than with any other medication. The other patient, who had infrequent but severe migraine attacks, was given 50 mg. intramuscularly when the onset of visual disturbance occurred. She then slept for several hours and

awoke refreshed and free of headache. Standard treatments given previously had failed to give more than slight symptomatic relief.

Six epileptics had fewer seizures when chlorpromazine was combined with standard anticonvulsants. Four have been free of seizures since starting this medication. Along with the decrease in the number of seizures there has been an increase in general well-being, and some of the patients felt they had been addicted. A depressed senile patient also benefited from treatment.

A small group of children with various behavioral disturbances all benefited markedly. The ages ranged from 2 to 13 years. A boy with laryngeal and facial tics was greatly helped by 25 mg. given four times daily. Hyperactivity associated with brain damage was completely controlled with similar doses. Another child whose numerous

TABLE 2.—*Summary of Results with Chlorpromazine Treatment in Psychiatry Hospital Patients (Group II)*

Diagnosis	Patients, No.	Therapeutic Response			
		Remission	Much Improved	Improved	Unchanged
Mania	18	11	5	0	2
Reactive depression	13	1	7	5	0
Endogenous depression	29	17	8	1	3
Total depression	42	18	15	6	3
Catatonic schizophrenia	9	5	2	2	0
Simple schizophrenia	1	0	0	0	1
Hebephrenic schizophrenia	6	3	2	1	0
Paranoid schizophrenia	33	13	9	9	2
Mixed schizophrenia	15	6	4	3	2
Total schizophrenia	64	27	17	15	5
Alcoholic delirium	23	22	1	0	0
Corticotropin delirium	1	1	0	0	0
Infectious delirium	1	1	0	0	0
Bromide delirium	2	2	0	0	0
Total delirium	27	26	1	0	0
Confusion, with cerebral disease	12	5	3	2	2
Epilepsy	4	1	1	1	1
Narcotic addiction, withdrawal symptoms	2	1	1	0	0
Stress reactions or psychotic episodes in psychopathic personalities	4	1	1	1	1
Hysteria	7	4	2	0	1
Anxiety neurosis	11	2	5	4	0
Total neuroses	18	6	7	4	1
Parkinson's disease	2	0	0	0	2
Status asthmaticus	1	0	1	0	0
Sydenham's chorea	1	0	1	0	0
Total	195	96	53	29	17

could work more effectively. One patient developed minor seizures in place of grand mal attacks.

The remaining patients in the ambulatory group include two in a confusional state following cerebral disease, one of whom benefited from taking the drug. Three patients were treated for postalcoholic tension states, with substantial improvement in two. Chlorpromazine eased the pain of a patient with osteogenesis imperfecta. He was able to forego meperidine (Demerol), to which he

fears, especially his fear of separation from his mother, had prevented his attending school cheerfully returned to school one week after he started treatment. It is noteworthy that children appear to tolerate adult doses of chlorpromazine with less side-effects than adults. The improvement in sleep and appetite is especially prominent.

Hospitalized Patients.—Table 2 summarizes the therapeutic response observed in this group.

The results achieved with 18 manic patients parallel those obtained by the French

and other European writers.§ Only two patients failed to show an improvement, and in one of these treatment was discontinued because of marked hypotension. One of the patients who recovered had been so exhausted by her manic excitement that she was almost moribund on admission. However, within three days after starting chlorpromazine she was quiet and rational. Two patients in this category were given electric shock therapy as well, but they required fewer than half the expected number of treatments to produce a clinical remission. This is of therapeutic significance, since manic patients are often resistant to lengthy courses of shock treatment. The average daily dose was 1,200 mg., given for 10 to 20 days. The recalcitrance of the manic condition often requires continuation of drug administration by the intramuscular route until improvement is well under way.

Depression, which may be regarded as the antithesis of mania, did not respond so dramatically. This is perhaps due to the side-effects of chlorpromazine—somnolence, reduction of activity, and asthenia—which appear to augment the depressive picture initially. Only when the patient becomes tolerant to these side-effects, or when the drug is withdrawn or reduced in dosage, is improvement apparent. Generally speaking, reactive depressions, being largely determined by adverse external circumstances, did not respond well, whereas patients with endogenous depressions, probably largely genetically determined, did almost as well as those in the manic group.‖ The treatment schedule was similar.

The therapy of schizophrenia is notoriously difficult to evaluate. Chlorpromazine, however, often produced dramatic reversals of symptoms and signs present for many years in these patients. The patients observed encompassed almost all the clinical variants of this polymorphous disease. As with other treatments, patient response to chlorpromazine was swifter and usually more lasting in cases in which the onset of illness was recent and sudden. Negro patients, who more commonly show this type of acute illness, did very well. Excited catatonic and paranoid patients tended to show an early response, particularly in regard to lessening of psychomotor activity and impulsive behavior. Restoration of normal biological rhythms of eating, sleeping, and elimination occurred in almost all cases. Those who were inaccessible because of mutism, fragmented speech, or overwhelming delusional and hallucinatory experiences became more communicative and would answer questions appropriately, though briefly. Some developed a degree of spontaneous insight into the psychodynamics of their symptoms. The persons classified as remitted not only lost abnormal activity and behavior but also reported disappearance of delusions and hallucinatory phenomena. Relatives described them as "better than they had been in years." Most patients continued to do well, although symptoms occasionally returned to some extent in the course of time. Paranoid schizophrenia, which customarily has a bad prognosis with other forms of treatment, responded well.

The dose of chlorpromazine required for schizophrenics has necessarily varied greatly. In the first stages of this study small doses were the rule. It has since been demonstrated that in chronic schizophrenia as much as 2 to 3 gm. daily must be given before beneficial effects are obtained. Surprisingly, patients receiving these large doses did not show a proportionate increase in the severity of side-reactions, with the exception of the Parkinsonian syndrome, which usually was observed only with the larger doses of the drug. Improvement in the chronic patients often took place by "crisis"; no change was noted until a certain individual threshold level was attained. Progress from then on was rapid. Occasionally a decrease followed by a sharp increase of chlorpromazine produced improvement in resistant cases. It is worth stating here that chlorpromazine dosages of

§ References 1-3.

‖ More recent experience with a larger number of depressed patients suggests that chlorpromazine is not as effective as herein indicated.

1,600 mg. daily and more may be abruptly terminated without ill effect, though there is usually transient hypertension and restlessness. Indefinite oral maintenance doses of 75 to 200 mg. a day were necessary in some of these patients. Omission of the drug for only a day or so caused return of symptoms in some. In others this dose was gradually decreased during the course of a month or two without impending signs of relapse.

Chlorpromazine was universally effective in 27 cases of delirium and toxic-confusional psychoses. Given in 50 mg. or 100 mg. doses every four to six hours it led to rapid clearing of symptoms within 24 hours in most cases. Some responded to a single dose, and others needed treatment for two or more days. Many patients with delirium tremens were discharged within three days of admission. A few hours in the emergency room sufficed for others. Not only were the confusion, hallucinations, and overactivity reduced, but general physiological disturbances of fever, tachycardia, anorexia, and toxicity promptly subsided. Three patients in this series were treated for more than one attack with equally good results. One patient with arthritis who became delirious following corticotropin (ACTH) therapy did well, as did one patient with delirium associated with postoperative sepsis. In spite of blood bromide levels of 500 mg. and 180 mg. per 100 cc., respectively, two delirious patients became rational within 48 hours.

Confusional states developing during the course of cerebral vascular disease, cerebral hemorrhage, and general paresis responded to chlorpromazine in eight cases. Not only was confusion dispelled in five patients but by having less tension and fewer complaints they became more comfortable than they had been for some time.

In conformity with a previous report,[13] chlorpromazine was found effective in relieving the narcotic withdrawal syndrome. One patient felt completely at ease on 200 mg. daily following abrupt termination of meperidine, which he had been taking in large doses for two years. In the other, moderate restlessness and insomnia was noted but neither of these symptoms appeared to disturb the patient to any extent.

Four epileptics with grand mal seizures were treated with chlorpromazine. One became seizure-free and has remained so for five months (previous seizure frequency was one a week); another showed marked improvement on chlorpromazine and diphenylhydantoin (Dilantin), though with either drug alone the seizures continued to occur. The third was slightly improved, and the fourth was made much worse. There were no cases of focal epilepsy.

Acute stress reactions or psychotic episodes accompanying a lifelong personality disorder responded well in two of four cases. Of the two remaining patients, one improved slightly but the other showed no significant modification of the underlying personality disorder, despite months of treatment.

Hospitalized neurotics were for the most part patients with chronic disease who had well-established somatization reactions. Some might be described as having psychosomatic disorders. Two patients with very acute anxiety or panic reactions were completely relieved when treated in a manner similar to the therapy for delirious patients. Four patients with an acute onset of hysterical convulsions, dissociative reactions, and major conversion symptoms responded promptly. Only one case with chronic conversion reaction showed marked improvement. The latter was a mechanic with a monoparesis who had received intensive psychotherapy for months without benefit. A patient with a history of rumination for nine months was adequately relieved. Those with multiple and diffuse complaints and with minimal tension were not greatly benefited even by massive doses.

In contrast to previous observations,[14] Parkinsonism failed to respond to chlorpromazine either in small or large doses. Both of the patients treated in this series were made worse. One later responded well to trihexyphenidyl (Artane), and the other, to diphenhydramine (Benadryl). The not infrequent development of Parkinsonism dur-

ing this treatment (see section on complications) anticipates this result.

A woman in the second trimester experienced attacks of status asthmaticus which yielded slowly to intravenous aminophylline, epinephrine (Adrenalin), and other standard treatments. An injection of 50 mg. of chlorpromazine terminated the attack within 30 minutes on three different occasions.

A 5-year-old girl with Sydenham's chorea was materially aided by 25 mg. of chlorpromazine injected four times daily. Its use was discontinued, however, because the induced tachycardia was feared to be prejudicial to her cardiac status.

Side-Reactions.—Daily doses of chlorpromazine of over 100 mg. always produced some side-effects at first, as did single doses of 50 mg. or more. Ten milligrams rarely produced noticeable changes. Hospitalized patients undergoing a typical course of chlorpromazine developed characteristic side-effects. They were always more noticeable with intramuscular medication. Sleepiness varied from short cat naps to deep somnolence throughout the greater part of the day and night. This resembled normal sleep in every respect. A few patients were given electroencephalograms, which revealed typical sleep patterns. The patient could always be aroused without much difficulty and on waking was rational (so far as the primary disorder permitted). Unlike most sedative agents, chlorpromazine, even in very large doses, did not lead to changes in the state of consciousness. Some patients spontaneously spoke of the refreshing nature of the sleep. Sleepiness usually decreased rapidly during the first few days of treatment in most patients, even on large doses. Four of the hospitalized patients developed an initial increase of tension and insomnia. There is no explanation for this, but all four of them had a history of anomalous responses to other drugs.

Hypotension occurred in all but a few cases in the hospitalized group of patients. There was frequently a drop of up to 60 mm. systolic and 40 mm. diastolic pressure. Decrease in blood pressure was more pronounced when the patient remained in an upright position. Some hypertensive persons became normotensive during treatment, but pressure returned to former levels later. The hypotension led to complaints of faintness and dizziness, which were more distressing when the patient stood up or stooped. The orthostatic hypotension, like the sleepiness, diminishes as treatment progresses and patients learn to avoid sudden movements. Both sleepiness and orthostatic hypotension occurred in the ambulatory patients to lesser degrees, but occasionally they caused enough annoyance that dosage had to be reduced. This was not the case with hospitalized patients.

Dryness of the oral and nasal mucosa was a common side-reaction, commented on by about half the patients. When nasal congestion was troublesome, antihistamine nose drops were found to be the most effective remedy. The patients were encouraged to chew gum for dryness of the mouth. A few patients complained of a bad taste in the mouth.

Of the gastrointestinal disturbances, constipation was the most frequent. This phenomenon was of direct benefit in those who were prone to diarrhea. Approximately 10% of the patients complained of heartburn following ingestion of the tablets. Simultaneous ingestion of procaine tablets relieved this. A small number developed frank nausea, and two patients vomited. This appeared to be due to a local irritant effect of the drug.

Interference with visual accommodation was quite frequent with high doses, and a few patients complained of diplopia as a transient phenomenon. Conspicuous miosis was seen in three patients.

A number of patients spoke of increased frequency of urination, particularly at night. Measurements of fluid balance were inconclusive. It is felt that frequency rather than diuresis is the explanation.

Chlorpromazine apparently disturbs central temperature regulation, as has been noted and utilized elsewhere.[4] A few of the patients in this study showed a drop in temperature. About half of those receiving doses of chlor-

promazine in excess of 600 mg. daily showed transient elevations of temperature. These were discovered on routine temperature charting. The patients rarely complained of or showed clinical signs of fever, although one patient had frank chills. In some cases the temperature was as high as 105 degrees. Occasionally this temperature elevation occurred several times daily, but more commonly it was an isolated phenomenon. The spikes were not accompanied by leucocytosis or other demonstrable cellular or biochemical changes.

observed. Sometimes this was associated with increased secretion of sebum. It usually decreased after the first few days.

Generalized weakness was commonly reported when large doses of chlorpromazine were given. There was no objective evidence of muscular weakness except in patients who developed Parkinsonism (see complications). In all likelihood this weakness represents a subjective description of the central inhibition of motor activity and drive produced by the drug.

TABLE 3.—*Summary of Results with Chlorpromazine in Treating Nausea and Vomiting Due to a Variety of Causes in 338 Patients* *

Etiology of Nausea and Vomiting	Patients, No.	Therapeutic Response				Side-Effects
		Excellent	Good	Fair	Poor	
Digitalis therapy	6	6	0	0	0	Varying degrees of drowsiness common but not incapacitating; diminishing as treatment went on; some dizziness and dryness of mouth; slight drop in blood pressure in 12%
Hexamethonium therapy	3	0	3	0	0	
Nitrogen mustard therapy	40	24	9	5	2	
Urethan therapy	2	1	0	1	0	
Antibiotic therapy	10	6	4	0	0	
Narcotics	6	6	0	0	0	
Veratrum viride	15	0	2	1	12	
Quinidine therapy	2	0	1	0	1	
Aminophylline therapy	6	4	1	1	0	
Aminopyrine therapy	1	0	1	0	0	
Total	91	47	21	8	15	
Infections	45	36	6	1	2	
Toxicosis	49	34	9	4	2	
Cardiovascular disease	8	7	1	0	0	
Gastrointestinal disease	32	24	3	4	1	
Spinal anesthesia	30	28	0	0	2	Potentiation of premedication
Pregnancy	78	55	14	5	4	
Miscellaneous	19	12	5	0	2	
Total	352	243	59	22	28	

* The majority of these patients comprised a previous report.[17]

Two patients who were receiving very large doses of chlorpromazine excreted sugar in the urine with normal blood sugar levels. This may or may not have been an unrelated finding.

Appetite was strikingly stimulated by large doses (and sometimes by small ones) of chlorpromazine. In several patients, who are not included in the series, this was utilized as a method for increasing their weight. Since many of the psychotic patients were chronically or acutely malnourished, this orexigenic effect had a decided advantage.

A chalky pallor of the skin of patients receiving large doses of chlorpromazine was

Moderate engorgement of the breast with secretion of colostrum was noted by 12 female patients in the hospitalized group. Two were convinced they had become pregnant, and their physician did not dispute this until time had disproved the pregnancy and established the connection with chlorpromazine. There were no menstrual irregularities associated with the treatment.

TREATMENT OF NAUSEA AND VOMITING

Table 3 summarizes our results with chlorpromazine used as an antiemetic in the treatment of 352 patients.

The cases studied represent a wide range of causes of nausea and vomiting, including

drugs, infections, toxemias, spinal anesthesia, and pregnancy. Response to therapy did not vary appreciably with the type of case treated. It was observed that in those patients failing to show an excellent response the dose employed and the routes of administration were approximately the same as in the patients who responded.

Observations were made on 91 patients experiencing nausea and vomiting associated with drug administration. It is apparent that chlorpromazine is an effective agent for the treatment of drug-induced nausea and vomiting. In contrast to results of laboratory observations, chlorpromazine was highly effective in arresting nausea and vomiting due to digitalis intoxication. Chlorpromazine was administered by the intramuscular route in four of six patients thus treated.

Of 40 patients being treated with nitrogen mustard, chlorpromazine failed to arrest the nausea and vomiting in only 2 instances; 5 patients remained quite nauseated but did not vomit, and 9 experienced nausea intermittently. Most of the patients in this group received at least three intravenous infusions of nitrogen mustard. Chlorpromazine was usually administered alternately during consecutive infusions of the mustard therapy. For example, during the first infusion it was given as treatment after the patient experienced nausea and vomiting. In those patients who experienced nausea and vomiting during the first infusion, chlorpromazine was given prophylactically during the second infusion (at least 24 hours after the first). During the third infusion chlorpromazine was again given as treatment after nausea and vomiting had been induced, in order to be reasonably sure that the patients would have continued to be nauseated on nitrogen mustard therapy. Patients who did not become nauseated during the third infusion were discarded from the study. It was felt that they would probably not have experienced nausea and vomiting with the second course of treatment even if chlorpromazine had not been used prophylactically. Chlorpromazine was equally effective whether given prophylactically or therapeutically. It was less effective orally when the patient was already nauseated and/or vomiting. However, if nausea and vomiting were first arrested by injecting it intramuscularly, the drug could then be continued by the oral route with equal effectiveness.

Chlorpromazine proved to be an effective agent for combating nausea and vomiting due to gastric irritation associated with aminophyllin and antibiotic administration. It was very successful in combating nausea and vomiting associated with morphine administration—an observation in keeping with laboratory findings.[8] It was ineffective in controlling the nausea and vomiting associated with the administration of veratrum derivatives.

Chlorpromazine appears to be an effective antiemetic agent when patients are nauseated and vomiting owing to infections or toxic reactions from systemic diseases of the noninfectious varieties. During the course of the current study, a minor epidemic of nausea and vomiting caused by infectious gastroenteritis occurred in Houston. In controlling such nausea and vomiting the drug appeared to be very effective, although concurrent manifestations such as weakness, diarrhea, and fever were unaffected. Only 2 of 26 patients with this disease failed to respond to the antiemetic effect of chlorpromazine.

The drug appeared to be equally effective when nausea and vomiting were associated with such systemic conditions (toxicosis) as metabolic disturbances, malignant disease, and renal failure. In the latter instance, small doses of the drug were used, because a greater degree of sedation was obtained, apparently owing to reduced excretion of the drug in the presence of impaired renal function. Patients with hepatic disease likewise appeared to be more responsive to the drug than were patients with normal hepatic function.

Nausea and vomiting associated with peptic ulcer were relieved in six of nine patients in whom the drug was employed. Of particular interest was the observation that vomiting associated with intestinal obstruction is also frequently blocked with chlorprom-

azine. This makes it imperative that the diagnosis be clearly established before chlorpromazine is administered; otherwise, a more serious diagnosis may be obscured at a critical time, since this agent must be considered as symptomatic treatment for nausea and vomiting and is in no way curative. Vomiting associated with obstruction of the upper intestinal tract was blocked less effectively than obstruction of the lower bowel.

The value of chlorpromazine to the anesthetist was well demonstrated. Nausea and vomiting in 13 patients following general anesthesia were relieved in all cases treated. Also, the drug was observed to block retching associated with spinal anesthesia. Chlorpromazine was administered to 23 consecutive patients with intractable nausea and retching originating during spinal anesthesia.[12] The spinal anesthetic agent usually was tetracaine (Pontocaine) hydrochloride, administered in doses of 6 to 12 mg. Generally, chlorpromazine was administered intravenously, for speed of action, although results with intramuscular injection were equally satisfactory. First, the effect on retching was noted; then, within 5 to 10 minutes after the injection was given, patients were asked whether their nausea was still present. There were only 2 failures in this series of 23 patients.[12] The first failure was a 28-year-old man who developed intractable nausea and retching under spinal anesthesia (tetracaine hydrochloride, 8 mg.) while undergoing insertion of an intramedullary rod in his femur. He received 25 mg. of chlorpromazine intravenously, but his nausea and retching continued unabated. The second failure was a 49-year-old man who developed intractable nausea and retching during spinal anesthesia (tetracaine hydrochloride, 9 mg.) for excision of a perineal urinary fistula. He also was given 25 mg. of chlorpromazine, but he obtained no relief. The remaining 21 patients experienced immediate relief of retching, and when asked shortly afterward about their nausea they reported that it had subsided. A hypotensive response to chlorpromazine was noted in four patients. These pressure changes did not alter the favorable antiemetic response to the drug.

In seven patients nausea and retching were purposefully induced by the surgeon tugging briskly three times on the patient's stomach. All became nauseated and retched. Chlorpromazine was then given, intravenously, in a dose of 12.5 mg., and the maneuver was repeated. Patient response, 5 to 10 minutes later, was noted. This series, in a sense, was controlled. The stimulus for inducing nausea and retching, gastric traction, was as constant as the several unbiased surgeons could manage. Of the seven patients so stimulated, none developed nausea and retching when pretreated with chlorpromazine, whereas all had previously developed nausea and retching when left untreated.

Nausea and vomiting of pregnancy responded very well to chlorpromazine. Of 78 patients treated, 55 obtained complete relief and only 4 were complete failures. The average period of treatment was two months, and the shortest period in the responsive patients was two weeks. Six patients continued to take the drug throughout the entire period of gestation. Sedation and dizziness were quite common during the first week of medication. Occasionally hypotensive episodes (syncope) were observed, especially following the initial doses of the drug, but these continued to be a problem in only two patients. The sedative effect could be easily controlled in most instances by giving 5 to 10 mg. of dextro-amphetamine (Dexedrine) sulfate concurrently with the chlorpromazine. The minimal effective dose of chlorpromazine, which was consistently dependable, appeared to be 25 mg. Although many patients responded to 10 mg., it frequently became necessary to increase the dose to 25 mg. before nausea and vomiting were checked.

Some of the patients began to vomit when they awoke in the morning, since the effect of the dose taken at bedtime had worn off. When vomiting in these patients prevented their taking chlorpromazine orally, it became necessary either to administer the first dose of the day by the intramuscular route or rec-

tal route (suppositories) or to have the patient take a 2:00 a. m. dose. With the latter, the patient could avoid a break-through of the drug's effect in the morning. The patients in this group (nausea and vomiting of pregnancy) had severe nausea and vomiting. Placebos were frequently used for evaluating drug effect, and there was rarely any doubt as to drug responsiveness or lack of it.

Side-Reactions.—In evaluating the side-effects produced by chlorpromazine when used in the treatment of nausea and vomiting it was found that of the 352 patients studied, 47% reported varying degrees of drowsiness; 23% developed dizziness; 19% developed a slight drop in blood pressure. There was no relationship noted between the cause of vomiting and the development of side-reactions. The sedation produced in the majority of cases was very mild and would not have interfered with the patients' normal activity. However, a few patients were quite sedated, and two were depressed when given 50 mg. intramuscularly so that they could not be awakened with prodding that would have awakened a person from natural sleep. None of the patients developed depression of this degree while receiving the drug orally, even in doses up to 100 mg. every four hours. Sedation was most marked during initial treatment and usually subsided to a considerable degree with continued drug administration. This was particularly evident in the obstetrical patients, who usually continued to take the drug for prolonged periods. In patients who experienced marked sedation, it was frequently possible to reduce the dose so that the antiemetic effect persisted without sedation being a problem.

Patients who reported dizziness, without appreciable sedation, were not made dizzy to an extent that it interfered with their normal activity. The dryness of the mouth was very mild and did not concern the patients. When tachycardia occurred, the pulse rate usually increased from 10 to 20 beats per minute. However, in the two patients who were partly anesthetized the pulse rate increased 30 to 40 beats per minute, respectively. The reduction in blood pressure which was observed was mild in most cases. However, in seven patients there was a fall in the pressure of 30 to 40 mm. of mercury; they became very dizzy in the upright position. In three cases the pressure went as low as 90 mm. of mercury systolic and 60 mm. of mercury diastolic. A maculopapular skin rash was observed in a fourth. However, these complications were all transitory. There was no evidence of gastrointestinal or hepatic dysfunction noted in any of the patients receiving chlorpromazine.

In comparing dosage and route of administration of chlorpromazine it was observed that a slightly greater percentage of patients demonstrated side-effects from the drug when it was given intramuscularly than when it was given orally. Sedation was the commonest side-effect. The degree of sedation was usually greater when an equivalent amount of the drug was given parenterally. Dizziness, dry mouth, tachycardia, and hypotension were seen more frequently after administration by the parenteral route than after administration by the oral route.

Results with Prolonged Therapy for Treatment of Nausea and Vomiting

Fifty-five of the patients (exclusive of the obstetrical patients) in this series received chlorpromazine for 5 days to 3 months, with an average course being approximately 10 days. The frequency of administration during this period ranged from once daily to once every three hours. Forty-four of the patients received 25 mg. or more per day. The overall control of nausea and vomiting was as follows: 30 (55%), excellent; 17, good; 7, fair, and 1, failure. Therefore, on a long-term basis the therapeutic effectiveness seemed to be qualitatively similar to the observations made on short-term treatment. After several days of therapy fall in blood pressure and syncope were diminished even though the dose had not been reduced. Moreover, the sedative effect was reduced. Patients who had previously been sedated now required small doses of barbiturates when insomnia occurred. However, the antiemetic effect and

the potentiating effect on opiates and central nervous system depressants remained unchanged.

Use in Treatment of Intractable Hiccoughs

During the course of these studies 10 patients with hiccoughs which had persisted for more than two days were given chlorpromazine. Three patients had hiccoughs associated with severe heart failure; two, with carcinoma; and three, with hiccoughs that followed genitourinary surgery. In two other patients the etiology was undetermined. In six patients hiccoughs were arrested within 20 minutes after the intramuscular administration of one 25 mg. dose of chlorpromazine. Two required a second dose to control their hiccoughs, and two did not respond to the drug. Most of the commonly available remedies for hiccoughs had been tried before chlorpromazine was administered to these patients.

Complications with Chlorpromazine Therapy

Four effects of chlorpromazine therapy will be dealt with separately, because, unlike the side-reactions mentioned previously, they may necessitate cessation of treatment. Their incidence is summarized in Table 4. All occurred in the psychiatric series.

Dermatitis appeared in 27 cases. In two the rash was of a maculopapular type. In six the area of distribution included the whole body. In the others it was confined to the arms, particularly extensor surfaces, chest, neck, and forehead. Pruritus was marked. Two patients showed a generalized erythema multiforme. One exhibited a localized nodular eruption on the phalanges. Another patient developed an acneiform eruption over the face with painful lesions on the gums and palate. Two patients suffered with a generalized exfoliative dermatitis. One was severely ill with high fever and delirium. He responded to corticotropin.

Most, but not all, of these persons gave a history of allergic responses to other drugs, foods, etc. The dermatitis typically became manifest during the second week of treatment. Only two patients who developed dermatitis were receiving less than 100 mg. daily; above this level there was no correlation between dosage and incidence of dermatitis. No local skin reactions were noted at injection sites aside from induration with reddening of the overlying skin.

Following cessation of chlorpromazine the rashes usually cleared within one week. In a few patients pruritus persisted, particularly if the patient exposed himself to sunlight. Recently we have observed that the rash often disappears spontaneously despite continued drug administration. Tripelennamine (Pyribenazmine) usually afforded adequate relief of the pruritus in these patients. Oddly enough, in those patients in whom chlorpromazine had been stopped, reinstitution of therapy after the skin had cleared did not lead to recurrence of the dermatitis.

Confusion, with disorientation, hyperactivity, and disorganized behavior of varying degree, was seen in four cases. Two patients were receiving as much as 1,600 mg. of chlorpromazine daily. Three were schizophrenics and had made excellent progress. In each the confusional episode occurred during the third week of treatment. It developed in the course of a few hours and cleared up within 24 hours after reducing the dose to 200 mg.

Table 4.—*Complications of Chlorpromazine Treatment in Psychiatric Patients*

	Hospital Patients, No.	Ambulatory Patients, No.	Grade		
			I	II	III
Dermatitis	19	8	16	9	2
Parkinsonism	14	0	5	5	4
Confusion	4	0	0	3	1
Jaundice *	1	0	0	1	0

* Only one such complication was seen by the authors in this study, but several others have been observed by authors elsewhere.

daily. In one patient it persisted for 10 days. No explanation is offered.

Fourteen patients developed a Parkinsonian syndrome. All were receiving doses above 800 mg. daily. All were under 40 years of age. In five of the patients the changes were mild — moderate tremor, muscular weakness, stooping posture, and diminution of accessory movements. Another five showed more severe changes, with typical pill-rolling tremor, some difficulty in articulation, and increased salivation. Four developed a classic picture of postencephalitic Parkinsonism, with masked face, open mouth dripping saliva, cogwheel rigidity of the limbs, total loss of accessory movements and extreme difficulty in articulating, dysphagia, and a typical posture and gait. In spite of the physical handicaps, these patients remained cheerful, and their original disease showed no tendency to relapse. In the mild and moderately severe cases, reduction of chlorpromazine dosage led to disappearance of the symptoms within a few days. In the four severe cases, complete recovery was delayed for as long as one month. It is worth commenting that 12 patients in this group made an excellent improvement in their original condition.

COMMENT

Pharmacology

Laboratory Observations. — Chlorpromazine has been studied in dogs and in humans for evidence of toxicity. The laboratory studies (acute) in animals consisted of cardiac output studies, renal hemodynamic studies, and determinations of the drug's effect on water and electrolyte excretion. The drug produced adrenergic blockade of variable degree.[15] It reduced the blood pressure by decreasing peripheral resistance, with a variable effect on cardiac output.[16] Sometimes the cardiac output increased initially, but, as larger doses were administered, the blood pressure declined steadily and cardiac output was also reduced. In doses of 10 mg. per kilogram all dogs showed a marked drop in blood pressure primarily on the basis of peripheral vasodilation, and in some instances there was an associated reduction in cardiac output.

The electrocardiographic studies showed some flattening of the T waves in three dogs when 10 mg. per kilogram of the drug was administered. These were minimal alterations and probably of little significance. However, a fourth animal showed splintering of the R wave at the 10 mg. dose, with a widening of the QRS complex and an increase in the QT interval. When the drug was administered in progressively larger doses, the dogs developed marked tachycardia, with electrocardiographic evidence of intraventricular block. Usually, when doses of 75 to 85 mg. per kilogram were administered over a period of one to two hours ventricular tachycardia developed.

There was no evidence of acute renal toxicity or of renal hemodynamic alterations. However, the drug, when administered parenterally, appeared to increase sodium and water excretion slightly. Most of the animals showed a slight reduction in blood pressure, which was not associated with a significant alteration in glomerular filtration rate, except in one instance in which the blood pressure decreased from 136 to 94 mm. Hg and the glomerular filtration rate decreased from 73 to 48 cc. per minute. However, renal blood flow in this same animal was not altered significantly. Although renal blood flow frequently varied from period to period after drug administration, this was an inconstant response and, if anything, tended to increase.

Clinical Observations.—The clinical toxicity and pharmacodynamic studies consisted of renal-function and hepatic-function tests ¶ and observations for electrocardiographic alterations and changes in the hemopoietic system. The only evidence suggestive of possible cardiac toxicity consisted of alterations in the electrocardiograms of two patients. However, these all occurred in seriously ill patients in whom the changes could have been due to the underlying disease. None of the 15 control subjects so studied showed changes in the electrocardiograms. The pulse rate increased in numerous instances, par-

¶ Reference 16 and unpublished data.

ticularly when the drug was given parenterally. One patient, who had diabetic acidosis associated with nausea, vomiting, and hypopotassemia, developed a partial auricular-ventricular block (Wenckebach phenomenon) while receiving chlorpromazine therapeutically. This persisted for several days while he was being given the drug, but it could never be clearly ascertained whether the arrhythmia was associated with the drug or was related to the underlying disease process and low serum potassium. A second patient developed a wandering pacemaker after receiving 10 mg. of chlorpromazine intramuscularly. However, this patient also had carcinoma of the liver associated with severe nausea and vomiting. The sulfobromophthalein (Bromsulfalein) test in this patient showed 46% retention. Several patients showed minor T-wave alterations. Therefore, there is no definite evidence of electrocardiographic alterations produced by chlorpromazine.

Electroencephalographic tracings showed no changes due to chlorpromazine, with the exception that the alpha rhythm tended to be better developed. In one case of cerebral dysrhythmia the electroencephalogram showed that the patient improved on chlorpromazine medication.

There was no evidence of renal toxicity found in the routine clinical laboratory studies. Hepatic-function studies were done on 15 control subjects and in 9 patients who received the drug therapeutically for nausea and vomiting. Several of the patients had liver disease prior to receiving the drug. None of these showed any evidence of progressive hepatic dysfunction. However, it was noted that patients with hepatic disease showed an increased responsiveness after having received the drug for one week.

Thirty-three psychiatric patients who received large doses of chlorpromazine were followed with serial liver-function tests for a period ranging from 4 to 10 weeks. Daily intake of chlorpromazine during the period of observation ranged from 200 to 2,000 mg. daily. Two of the patients had evidence of liver disease at the start of treatment. None of the patients exhibited clinical signs of hepatic dysfunction or significant deviation from normal in the battery of liver-function tests employed. Those with abnormal readings at the start of treatment, due to liver disease or other cause, showed progressive improvement of hepatic insufficiency under the chlorpromazine regimen.

Despite the absence of toxicity in the controlled studies, jaundice has been observed by the authors in one instance in this series and in several patients treated elsewhere.

D. D.,# a 40-year-old woman, was seen because of anxiety, hypochondriasis, and intermittent depression. She was started on chlorpromazine, receiving 50 mg. four times daily for two weeks. Suddenly, she developed jaundice associated with extreme itching of the skin, epigastric tenderness, acholic stools, dark urine, nausea, and vomiting. The patient was moderately jaundiced, and the liver was slightly tender and palpable 2 cm. below the costal margin. The laboratory studies on admission were as follows: Alkaline phosphatase, 17.6 units; cephalin flocculation at 48 hours, 1 +; thymol turbidity, 1.8 units; prothrombin, 100%; serum bilirubin, 5.4 mg.; urinary urobilinogen, trace, and marked bilirubinuria. A complete blood cell count was within normal limits.

The patient was placed on bed rest, with considerable symptomatic improvement. Two weeks later the laboratory studies were repeated, with the following results: Alkaline phosphatase, 11 units; serum bilirubin, 2.9 mg.; thymol turbidity, 1.8 units, and the urine showed a trace of bilirubin. The blood cell count continued normal.

A liver biopsy showed bile stasis, with cholangiolitic obstruction and hepatic infiltration of lymphocytes without evidence of hepotocellular destruction (Fig. 1). Recovery was uneventful, and liver-function studies after one month were all within normal limits.

Preliminary psychometric studies appear to confirm the fact that the drug does not exert an effect on the cerebral cortex. Changes in psychological functioning due to inhibition of drive are quite apparent. Aside from this, however, behavioral effects have so far eluded measurement.

Clinical Use in Neuropsychiatry

The potential of chlorpromazine in treating the whole range of mental disorders ap-

Case reported through the courtesy of Dr. Hugh Hanson, Houston, Texas.

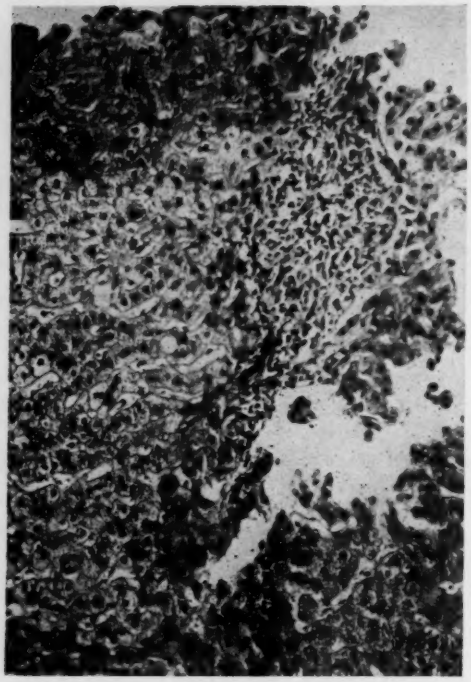
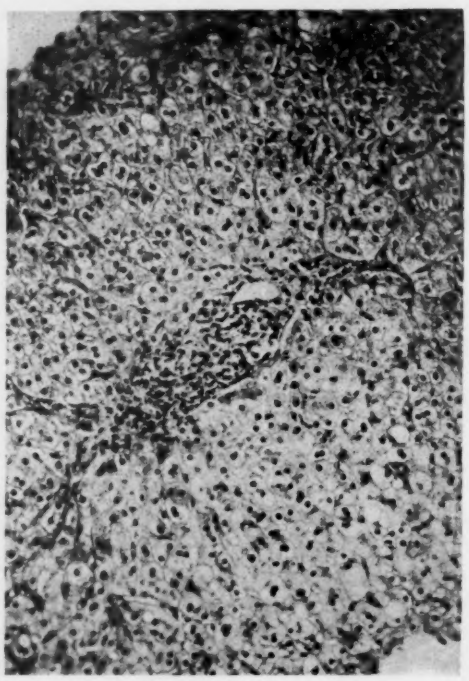


Fig. 1.—Liver biopsy specimen taken two days after patient was admitted to hospital with jaundice due to chlorpromazine. The biopsy shows marked lymphocytic and polymorphonuclear infiltration into the periportal space (upper right hand corner). Except for focal vacuolization there is no evidence of hepatocellular damage.

pears to be great, but as yet only the fringes have been explored. The drug has been used therapeutically in quantities ranging from as little as 15 mg. daily to 4 gm. a day. The necessity for the adjustment of dosage to the disease under treatment is quite apparent. It must be admitted that only tentative formulations can be made at this time. It has developed, for instance, that the large doses now being used with psychotic patients are much more effective than the initial small ones. On the other hand, the reverse has been true for minor emotional disturbances. At best, the doses cited above may be regarded as approximate guides. Initial intramuscular administration is always more effective in starting progress and should probably be used with all psychotic or seriously ill patients. Even later on during the course of treatment a few intramuscular injections may overcome a temporary lag in progress. Intramuscular injections are often painful. The discomfort has, at times, been alleviated by using a solution of 10 mg. per cubic centimeter, prepared by diluting the commercially available preparation (25 mg. per cubic centimeter) with saline solution. One per cent procaine has been used as a diluent in some cases, with encouraging results, but sensitivity reactions to the anesthetic have been encountered. In no case did the injection site undergo abscess formation, and the induration dissipates within a few days. Intravenous administration is not advised for routine use. Because of the lack of a satisfactory quantitative measure of plasma chlorpromazine, spacing of doses has been arbitrarily set at four- to six-hour intervals. Tolerance to the therapeutic effects of chlorpromazine has been noted in only one or two cases. On the contrary, it is nearly always

Fig. 2.—Liver biopsy specimen taken from the same patient two weeks after the specimen shown in Figure 1. There is a marked reduction in the lymphocytic and polymorphonuclear infiltration. Vacuolization has decreased, and the liver cells are now normal.



possible to reduce the dose as improvement progresses, with continued good effect. Of course, the drowsiness and hypotension do diminish greatly after a few days. Ambulatory patients are told of these side-effects and to expect their occurrence and subsequent disappearance in a short while.

Duration of treatment is equated with the patient's progress. On the whole, the more chronic the condition (psychotic or neurotic) the longer the required course. This has extended to nine months in some, and all indications are that it could be continued indefinitely if necessary. Some patients seem to require a certain daily amount of chlorpromazine in a manner which is analagous to the needs of the diabetic for insulin. If this need is not met, relapse follows swiftly.

Although no systematic study has been undertaken, a number of patients selected at random have been, without their knowledge, given placebos identical in appearance to chlorpromazine, for a few days. In all, except one case of tension state on small doses, the difference was detected both by the patient and by the clinician.

Patients on large doses of oral or intramuscular medication should be kept at rest for the first few days in order to avoid fainting and falling. Most persons learn by experience how soon they can get up and about. It is not imperative to record vital signs frequently, but daily recording of blood pressure and temperature should be made while dosage is being increased steeply.

Aside from the specific therapeutic effects of the drug, there are several general advantages worth mentioning. Violent and suicidal patients may be safely managed on an open ward, once chlorpromazine has taken effect. The noisiness and prison-like atmosphere, often characteristic of psychiatric wards, are absent. Personnel requirements are reduced. Physical restraint has been abandoned. Orders for sedatives have been drastically curtailed. This is additionally true of the ambulatory patients. There are no absolute contraindications to chlorpromazine. Barbiturates and opiates are potentiated by the substance; therefore, chlorpromazine should be cautiously given to anyone known to have taken large amounts of barbiturates. The respiratory depressant effects of morphine are considerably augmented. The presence of liver disease should engender cautious use of the drug. Though these patients have been treated successfully, the repeated occasional occurrence of jaundice indicates the need for careful observation. Hypotension of marked degree before treatment might be a deterrent factor. One patient with decompensated cardiac disease and several with high-grade hypertension have sustained large doses without incident.

Treatment of Nausea and Vomiting and Intractable Hiccoughing

For the routine use of chlorpromazine, an oral dose of 25 mg. or less should be used, to keep side-effects to a minimum. However, when the dose is dropped much below 25 mg. the drug is not as effective. Consequently, the usual effective dose is 25 mg. when taken by mouth. This can be adjusted up or down as therapy continues, depending on the response of the patient. However, the best procedure in managing the ambulatory patient is to use an initial 10 mg. dose. If this dose is therapeutically ineffective and side-reactions are not marked, then the dose can be increased to 25 mg. When the drug is given in 25 mg. doses intramuscularly or in 50 mg. doses either orally or intramuscularly, the patient should be kept at rest initially because of the occasional development of orthostatic hypotension to the point of syncope. The frequency of drug administration is usually every four hours, but this must be increased or decreased depending on effectiveness.

Conclusions

Chlorpromazine has been found to have wide application in neuropsychiatry.

In large doses it is an effective inhibitor of psychomotor excitement and agitation. It appears to have a stabilizing effect upon mood.

In both acute and chronic cases of schizophrenia it has brought about total disappearance of symptoms for as long as one year.

In small doses it produces marked alleviation of symptoms in the neuroses and other minor emotional disturbances.

It appears to have some anticonvulsant activity.

Chlorpromazine was found to be an effective antiemetic agent for a wide range of clinical conditions complicated by nausea and vomiting.

No dangerous side-effects have been observed.

REFERENCES

1. Hamon, J.; Paraire, J., and Velluz, J.: Remarques sur l'action du 4560 R. P. sur l'agitation maniaque, Ann. méd.-psychol. **110**:331-335 (March) 1952.

2. Delay, J.; Deniker, P., and Harl, J. M.: Utilisation en thérapeutique psychiatrique d'une phénothiazine d'action centrale élective (4560 R. P.), Ann. méd.-psychol. **110**:112-117 (June) 1952.

3. Lehmann, H. E., and Hanrahan, G. E.: A New Inhibiting Agent for the Control of Psychomotor Excitement, A. M. A. Arch. Neurol. & Psychiat. **71**:227-237 (Feb.) 1954.

4. Kinross-Wright, V.: Chlorpromazine Treatment of Mental Disorders, Am. J. Psychiat., to be published.

5. Winkelmann, N. W., Jr.: Chlorpromazine: A New Drug in the Treatment of Neuropsychiatric Disorders, J. A. M. A. **155**:18-21 (May 1) 1954.

6. Kinross-Wright, V.: Chlorpromazine: A Major Advance in Psychiatric Treatment, Postgrad. Med. **16**:297-299 (Oct.) 1954.

7. Moyer, J. H.; Kent, B.; Knight, R. W.; Morris, G.; Dizen, M.; Rogers, S., and Spurr, C.: Clinical Studies of an Antiemetic Agent, Chlorpromazine, Am. J. M. Sc. **228**:174-189 (Aug.) 1954.

8. Cook, L., and Toner, J. J.: The Antiemetic Action of Chlorpromazine, SKF No. 2601-A (RP-4560), J. Pharmacol. & Exper. Therap. **110**:12 (Jan.) 1954.

9. Boyd, E. M.; Cassell, W. A., and Boyd, C. E.: Prevention of Apomorphine-Induced Vomiting by (Dimethylamino-1-N - Propyl-3) - N - (2 Chloro)-Phenothiazine Hydrochloride, Fed. Proc. **12**:303 (March) 1953.

10. Brand, E. D.; Harris, T. D.; Borison, H. L., and Goodman, L. S.: The Antiemetic Activity of 10-(γ - Dimethylaminopropyl) - 2 - Chlorphenothiazine (Chlorpromazine) in Dog and Cat, J. Pharmacol. & Exper. Therap. **110**:86-92 (Jan.) 1954.

11. Jentzer, A.: Hibernation, anesthésie potentialisée, choc post-opératoire à l'exclusion de l'hypotension contrôlée, Schweiz. med. Wchnschr. **82**: 1215-1219 (Nov. 22) 1952.

12. Mathews, W.; Morris, G., and Moyer, J. H.: Potentiation of Anesthetics with Chlorpromazine, to be published.

13. Staehelin, J. E., and Kielholz, P.: Largactil, ein neues vegetatives Dämpfungsmittel bei psychischen Störungen, Schweiz. med. Wchnschr. **83**: 581-586 (June 20) 1953.

14. Lehmann, H. E.: Selective Inhibition of Affective Drive by Pharmacological Means, Am. J. Psychiat. **110**:856-857 (May) 1954.

15. Courvoisier, S.: Fournel, J.; Ducrot, R.; Kolsky, M., and Koetschet, P.: Propriétés pharmacodynamiques du chlorhydrate de chloro-3(diméthylamino-3'-propyl)-10 phénothiazine (4,560 R. P.): Étude expérimentale d'un nouveau corps utilisé dans l'anesthésie potentialisée et dans l'hibernation artificielle, Arch. internat. pharmacodyn. **92**: 305-361 (Jan.) 1953.

16. Moyer, J. H.; Kent, B.; Knight, R.; Morris, G.; Huggins, R., and Handley, C. A.: Laboratory and Clinical Observations on Chlorpromazine (SKF 2601-A): Hemodynamic and Toxicological Studies, Am. J. M. Sc. **227**:283-290 (March) 1954.

17. Moyer, J. H.; Kent, B.; Knight, R. W.; Morris, G.; Dizon, M.; Rogers, S., and Spurr, C.: Clinical Studies of an Anti-Emetic Agent, Chlorpromazine, Am. J. M. Sc. **228**:174-189 (Aug.) 1954.

USE OF PLANIGRAPHY IN DEMONSTRATION OF CALCIFICATION OF HEART VALVES AND ITS SIGNIFICANCE

LOUIS A. SOLOFF, M.D.
JACOB ZATUCHNI, M.D.
and
HERBERT FISHER, M.D., Philadelphia

PRESENT-DAY popularity of surgery for cardiac valve disease of acquired origin has made precise diagnosis of valve lesions of the utmost importance. Success of surgery may depend, among other factors, upon the nature of the pathologic changes within the valve itself and upon the total number of valves involved. Our anatomic studies have shown how often associated valve lesions are overlooked in the presence of mitral valve disease.[1] These findings likewise have emphasized the importance and the frequency of multivalvular lesions in persons with rheumatic heart disease who die and particularly those who die of congestive heart failure. By implication, these findings have further emphasized the well-known fact that murmurs which are so frequently characteristic of specific valve lesions may also be uncharacteristic for them. A single murmur may represent an auditory fusion of murmurs originating from several valve abnormalities. Moreover, with changing cardiac function, murmurs may change their specific characteristics and their location and may even disappear. Lastly, a murmur by itself rarely gives insight into the pathologic disturbance within the valve. Yet, there is no doubt that murmurs are of the utmost importance in the diagnosis of valve disease, because virtually all other findings, although suggestive, are less characteristic. The one exception, when present, is calcification of a valve.

Calcification within a heart valve is an absolute and irreversible manifestation of valve disease. Moreover, it is specific for the valve involved. It indicates that the valve, in part at least, is composed of dead tissue and is surrounded by a zone of avascular, fibrous tissue, changes that imply a disturbance in pliability and mobility and potential regurgitation that may not be wholly correctible by present-day surgical techniques. Furthermore, we have shown that calcification of the mitral valve is not found at death as a lone valve lesion.[1] The possibility of an associated valve lesion during life in a person with a calcified mitral valve is probably very high.

Planigraphy is superior to all other methods so far used for obtaining permanent and verifiable records of valve calcification.[2] Moreover, it is harmless to the patient, a quality that unfortunately is lacking in many diagnostic techniques recently introduced into cardiology. By this method, we have been able also to demonstrate atrial calcification totally unsuspected by all other diagnostic methods.

The purpose of this paper is to show the value of planigraphy (1) in the uncovering of unsuspected multivalvular lesions, (2) in the discovery of valve calcification in otherwise unexplained cardiomegaly, and (3) in the preoperative evaluation of patients for intracardiac valve surgery.

MATERIAL AND METHODS

Thirty-one patients were studied. All were on the medical service of one of us or were seen in consultation for cardiac evaluation or for treatment or for both.

From the Departments of Medicine, Temple University Medical School and Hospital and Episcopal Hospital, and the Department of Radiology, Episcopal Hospital; Clinical Professor of Medicine, Temple University Medical School and Hospital, and Chief of Medicine, Episcopal Hospital (Dr. Soloff); Associate in Medicine, Temple University Medical School and Hospital and Episcopal Hospital (Dr. Zatuchni); Director, Department of Radiology, Episcopal Hospital (Dr. Fisher).

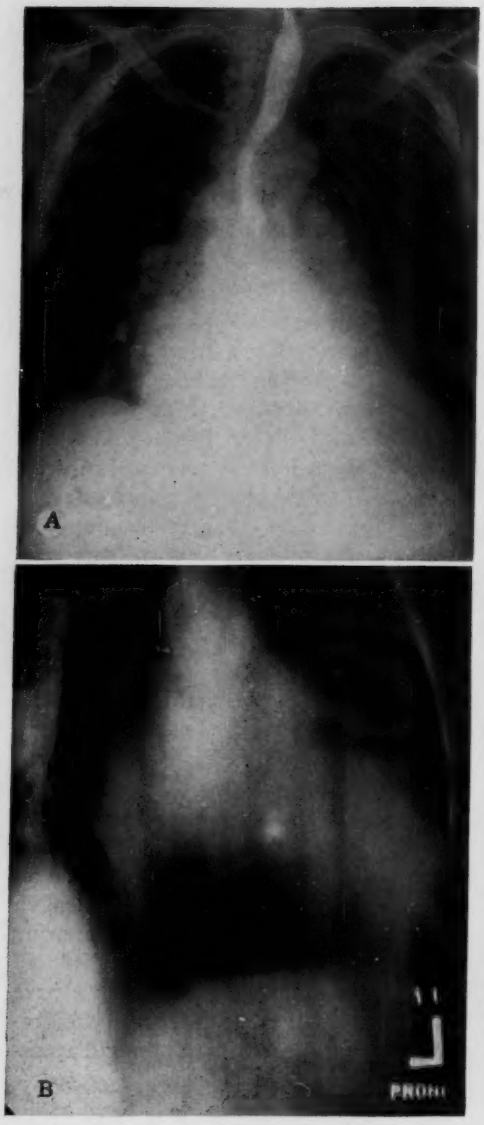
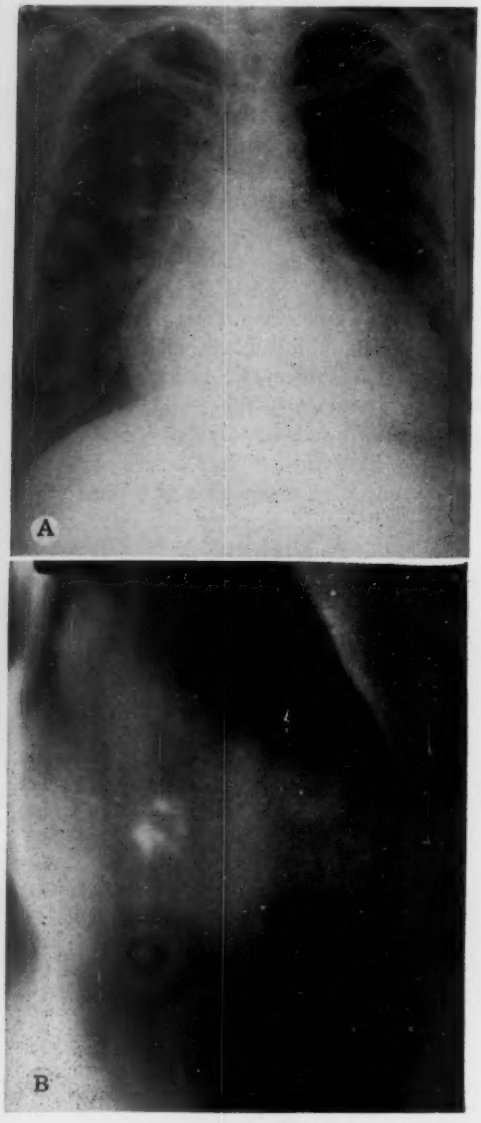


Fig. 1 (Patient L. S.).—*A*, chest roentgenogram (P-A projection) of a 56-year-old woman with hypertension and an aortic diastolic murmur. There was no history of rheumatic fever. No intracardiac calcification is seen. *B*, planigram of heart, left lateral projection, 11 cm. from the table top, showing calcification of the mitral valve that is seen on a level with the lower border of the left atrium.

Sixteen were candidates for mitral valve surgery. Of the other 15, all with cardiomegaly, 12 had a precordial systolic murmur and 2 had aortic regurgitation. The remaining one had no murmurs. This one, a woman, 70 years old, had recurrent bouts of atrial tachycardia of 15 years' duration. A diagnosis of intrinsic heart disease was never made. Of the two with aortic regurgitation, one is 63 years old and has known rheumatic heart disease and the other is 56 years old and has hypertension but no history of rheumatic fever. In the former, associated mitral valve disease could not be excluded by physical findings, and in the latter

Fig. 2 (Patient C. Z.).—*A*, chest roentgenogram (P-A projection) of a 62-year-old woman with aortic stenosis. No intracardiac calcification is seen. *B*, planigram of heart, RAO projection, 12 cm. from the table top, showing calcification of the aortic valve that is seen in the midportion of the cardiac density in relation to the ascending aorta.



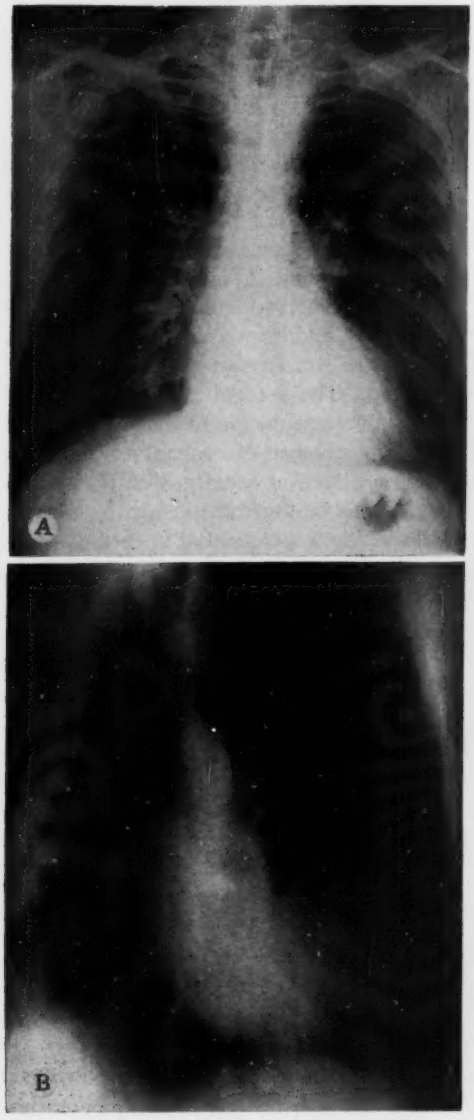


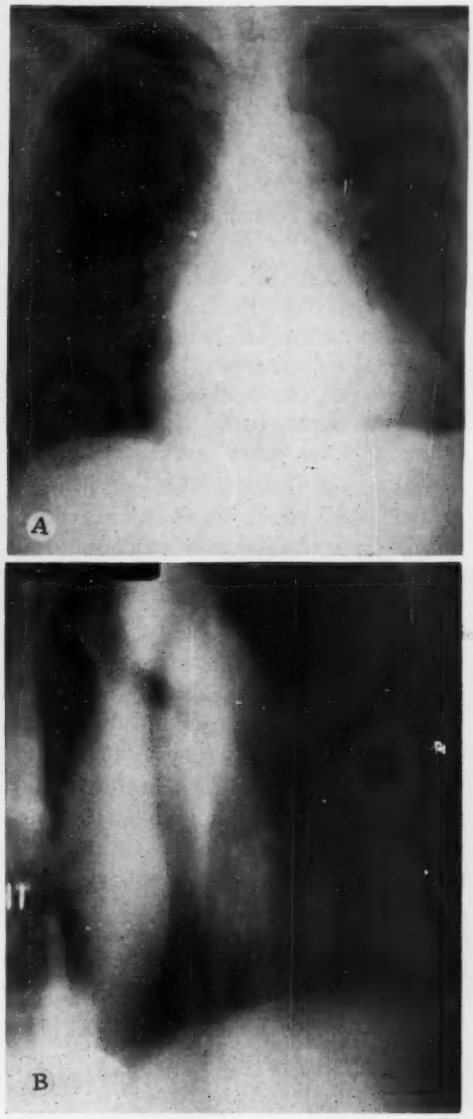
Fig. 3 (Patient J. H.).—*A*, chest roentgenogram (P-A projection) of a 52-year-old man with coarctation of the aorta and a precordial systolic murmur that was attributed to the anomaly. No intracardiac calcification is seen. Note the notched ribs and the small aortic knob and its irregular contour. *B*, planigram of heart, RAO projection, 8 cm. from the table top, showing calcification of the aortic valve, which established the diagnosis of associated aortic valve disease.

the murmur was thought to be unusual for hypertensive disease alone.

Of the 12 with a precordial systolic murmur, all were 52 years of age or older. None had a history of rheumatic fever. One had coarctation of the aorta. Seven had sinus rhythm, and five had atrial fibrillation. A clinical diagnosis of aortic stenosis was made in all except the one with coarctation of the aorta, whose murmur was attributed to the anomaly.

Of the 16 candidates for mitral valve surgery, all had an apical diastolic rumbling murmur and all

Fig. 4 (Patient L. S.).—*A*, chest roentgenogram (P-A projection) of an 83-year-old man with a clinical diagnosis of aortic stenosis and atrial fibrillation. No calcification is seen. *B*, planigram of heart, RAO projection, 14 cm. from the table top, showing calcification of the aortic and mitral valves, which was confirmed at necropsy.



but one had a mitral systolic murmur of Grade 2 intensity or less. Additional murmurs, aortic in location, were present in two. Nine had sinus rhythm, and seven, atrial fibrillation. A clinical diagnosis of mitral stenosis was made in all, and, in addition, two had a diagnosis of aortic stenosis.

Planigraphic studies, in addition to conventional roentgenograms, were made of each patient. Two had two studies. The projections used included the left lateral in 7, left posterior oblique in 2, left anterior oblique in 1, and right anterior oblique in 23. Sections were made usually at intervals of 1 cm., occasionally at 0.5 cm., at a distance varying from 6 to 15 cm. from the table top.

RESULTS

In the patient who had bouts of atrial tachycardia and cardiac enlargement of undetermined etiology, planigraphy demonstrated calcification of the aortic and mitral valves. Valve disease was never suspected clinically, and reexamination revealed no murmurs.

Of the two patients with aortic regurgitation, the one with rheumatic heart disease was shown to have calcification of the aortic and mitral valves, although a clinical diagnosis of aortic disease alone was made. The other, the patient with hypertension, was shown to have mitral valve calcification, which is illustrated in Figure 1.

Of the 12 patients who had a precordial systolic murmur, valve calcification was demonstrated by planigraphy in 11. Of these, all had calcification of the aortic valve, which is illustrated in Figures 2 and 3, and six had calcification of the mitral valve also, which is illustrated in Figure 4. Necropsy, done in three of four who died, confirmed the presence and extent of valve calcification.

Of the 16 candidates for mitral valve surgery, intracardiac calcification was demonstrated by planigraphy in 12. Of these 12, all had calcification of the mitral valve, and, in addition, there was calcification of the aortic valve in 1 and of the wall of the left atrium in 3. Surgery was done in 9 of the 12, and the presence of calcification was confirmed in each. Of the four without calcification, one died. No calcification was seen at necropsy.

Thus, 26 of the 31 patients examined were shown by planigraphy to have intracardiac calcification. Nine had calcification of the mitral valve alone; three, of the mitral valve and left atrium; nine, of the mitral and aortic valves, and five, of the aortic valve alone.

COMMENT

Valve calcification is readily recognized in planigraphic films. Calcification stands out in marked contrast to the surrounding cardiac density, and its position is easily located, because the cardiovascular landmarks are preserved. The recognition of calcification by other roentgenologic methods is difficult because of absence of contrast or superimposition of extracardiac densities. These difficulties may be overcome in part by the use of the coning technique that in turn depends upon fluoroscopy for the location of the calcification.[8] Yet calcification may be missed at fluoroscopy, particularly in the presence of cardiomegaly and even when done with proper dark-adaption by persons with interest in and knowledge of the subject. Indeed, in this study, fluoroscopy done by us revealed no calcification in three patients and incomplete findings in an additional six. The planigram, on the other hand, has not only the highest positive yield but also the additional advantage of providing permanent evidence of the presence of intracardiac calcification that can be verified by others. Valve calcification demonstrated by planigraphy in this study was confirmed in every instance that came to operation or autopsy.

It is significant that of the nine patients with calcification of both the aortic and mitral valves only two had a clinical diagnosis of combined valve disease. Of the remaining seven, six were thought to have aortic stenosis alone because of the presence of a precordial systolic murmur only and one, without murmurs, was not even suspected of having valve disease.

In two patients the demonstration of valve calcification was the basis for a diagnosis of heart disease previously unsuspected. Each had a murmur that was attributed to periph-

eral vascular disease, hypertension in one case and coarctation of the aorta in the other.

The finding of valve calcification is significant not only because of the uncovering of valve disease where none is suspected but also because it implies the nature of the valve deformity. All of the patients with valve calcification who died had valve stenosis. Moreover, the surgeon found the mitral orifice to be small in each of the nine patients with calcification of the mitral valve who had surgery. But, of greater significance, eight of the nine had a regurgitant jet before surgery and in four of these it was increased by surgery. In none did the regurgitant jet lessen after surgery. In the one without a jet, a mitral systolic murmur, in addition to preexisting murmurs, appeared in the postoperative period and has remained to the present time, two years after surgery.

Valve calcification may also be associated with an increased risk of surgically-induced thromboembolism, regardless of the presence of atrial thrombi. Indeed, of the nine patients in this study who had surgery, one died. Calcification of the mitral and aortic valves demonstrated by planigraphy was confirmed at surgery. No intracardiac thrombus was present. The patient never recovered consciousness after surgery and died two days later of a cerebral embolism. Of the remaining eight, thrombi were found in the left atrium or its appendage in four, in three with calcification of the mitral valve alone and in one with additional calcification of the left atrium. In none of these could the surgeon remove the thrombotic masses.

On the basis of these findings, it appears that a search for intracardiac calcification by planigraphy is of value (1) in otherwise unexplained cardiomegaly, (2) to detect other valve lesions when calcification of one valve is seen by other roentgenologic techniques, (3) to detect mitral valve disease when aortic valve disease has been diagnosed, (4) for elucidating the source of murmurs of uncertain origin, and (5) as a simple screening method in the selection of candidates for mitral valve surgery.

Many years ago, Cutler [4] wrote "it seems, furthermore, that a slit-like cut in the markedly thickened valve, on account of the stiffness and rigidity of the incised margins, may relieve the functional obstruction but little." Such a statement appears particularly applicable to a valve that has sufficient calcium to cast a shadow upon a film. Examination at autopsy of such valves that have been sectioned during life strengthens this opinion. Moreover, operative interference in the case of such valves increases the incidence of embolization and the incidence and degree of mitral regurgitation.

SUMMARY AND CONCLUSIONS

Planigraphic studies of the heart in 31 patients revealed calcification of the mitral valve alone in 9, of the mitral valve and left atrium in 3, of the mitral and aortic valves in 9, and of the aortic valve alone in 5.

Multiple valve lesions were disclosed where none or only one was suspected by all other methods.

Valve lesions were discovered in those with cardiomegaly or precordial murmurs of uncertain origin.

Calcification of the mitral valve usually produces mitral stenosis and regurgitation.

Such calcification increases the risk of the production of more regurgitation and of embolism by mitral commissurotomy.

REFERENCES

1. Soloff, L. A., and Zatuchni, J.: Cause of Death of Individuals with Rheumatic Heart Disease and Its Relationship to Mitral Stenosis Occurring Alone or in Combination with Other Valve Lesions, Am. J. Med., to be published.

2. Soloff, L. A.; Zatuchni, J., and Fisher, H.: Visualization of Valvular and Myocardial Calcification by Planigraphy, Circulation **9**:367, 1954.

3. Sosman, M. C., and Wosika, P. H.: The Technique for Locating and Identifying Pericardial and Intracardial Calcification, Am. J. Roentgenol. **50**:461, 1943.

4. Cutler, E. C.; Levine, S. A., and Beck, C. S.: The Surgical Treatment of Mitral Stenosis: Experimental and Clinical Studies, Arch Surg. **9**:689, 1924.

STUDIES ON URINARY LIPASE

I. On a Fat-Splitting Enzyme in Urine and Its Relation to Pancreas

MARTIN M. NOTHMAN, M.D.
JOSEPH H. PRATT, M.D.
and
ALLAN D. CALLOW, M.D., Boston

THE NUMBER of studies on fat-splitting enzymes in the urine is very small. Papers on urinary enzymes in general hardly mention the possibility of their presence. The methods used are open to objection. It is, therefore, not surprising that the results are contradictory. The latest and rather comprehensive German paper, by Zorn,[1] published in 1937, denies the presence of a fat-splitting enzyme in the urine of healthy persons. In the American literature of the past 20 years we did not find any reference except for a citation of Zorn in Bockus' "Handbook of Gastroenterology."[2]

In our early investigation of pancreatic enzymes in blood and urine under normal, pathological, and experimentally produced conditions in men and animals [3] we developed a method for the determination of a fat-splitting enzyme in the blood and adapted it for the use in the urine. The principle of the method is that lipase splits olive oil to fatty acids and glycerine. The fatty acids thus liberated are measured by titration against a standard sodium hydroxide solution.

METHOD

In detail, the method used for the determination of the fat-splitting enzyme in the urine of dogs is as follows:

Five cubic centimeters of urine is brought to a pH of about 7.3 with Sörensen M/15 phosphates mixtures.[4] In general, 10 cc. of the phosphate buffer will be sufficient. Three blanks are utilized for every determination: B_1 represents the urine blank; B_2 the olive oil blank, and B_3, the buffer blank.

B_1	B_2
2 cc. H_2O	2 cc. oil emulsion
5 cc. calcium acetate	5 cc. calcium acetate
5 cc. buffer	5 cc. buffer
3 cc. urine phosphate buffer mixture (equivalent to 1 cc. urine)	3 cc. H_2O
B_3	Test
5 cc. H_2O	2 cc. oil emulsion
5 cc. calcium acetate	5 cc. calcium acetate
5 cc. buffer	5 cc. buffer
	3 cc. urine phosphate buffer mixture

Mix B_2 and tests thoroughly in a shaker for 10 minutes. Incubate the four flasks at 37 C. for 24 hours. At the end of incubation add 10 cc. of alcohol-ether inactivating mixture to each flask. After having added a few drops of phenolphthalein, titrate with N/20 NaOH to definite pink. Calculation: Add B_1 to B_2 and subtract B_3. Finally, subtract this result from the test.

Example:					
B_1	3.0	B_1	3.0	Test	3.65
B_2	0.25	B_2	+0.25		−3.15
B_3	0.1		3.25		0.50
Test	3.65	B_3	−0.1		
			3.15		

Reagents.—Olive Oil Emulsion: Gum acacia, 12.5 gm.; olive oil, 50 cc.; H_2O, 100 cc. Pour the gum acacia and 50 cc. of H_2O into a Waring Blendor and thoroughly mix. Then add the olive oil slowly and allow to mix to a pure white emulsion. Then add 50 cc. more H_2O and mix to a uniform consistency. Store in the icebox.

Calcium Acetate: Ca $(C_2H_3O_2)$ 2 H_2O. Calcium acetate, 20 gm.; liter of H_2O.

Barbiturate Buffer: Sodium diethylbarbiturate, 0.1 gm. per liter of H_2O.

Alcohol-Ether Inactivating Mixture: Alcohol 95%, 900 cc.; ether, 100 cc.

PROCEDURE AND RESULTS

Our findings are based on observations on dogs. Animals weighing from 6 to 12 kg. were used. We determined the fat-splitting enzyme in the urine in about 150 samples of 20 normal untreated dogs. A fat-splitting enzyme was regularly present. The values found ranged from 0.15 to 1.0 units. This

From the Medical and Surgical Departments of the New England Center Hospital and Tufts College Medical School.

Supported by a grant-in-aid from the American Cancer Society upon recommendation of the Committee on Growth of the National Research Council and by a grant from the Charlton Research Fund, Tufts College Medical School.

means that after incubation of the solution for 24 hours between 0.15 cc. and 1.0 cc. of N/20 NaOH have been necessary for the titration of the liberated fatty acids to a pink end-point with phenolphthalein. It did not make any difference whether the urine was collected in the morning when the dogs were still fasting or two to four hours after the feeding. The value of the fat-splitting enzyme in the urine is, it appears, about the same as the value for the lipase in the serum.

Since we have proved [8] that serum lipase is, at least predominantly, of pancreatic origin, we attempted to clarify the relationship between the fat-splitting enzyme in the urine and the pancreatic gland. For this purpose the following series of experiments was performed:

1. The effect of secretin and methacholine (Mecholyl) on the excretion of the fat-splitting enzyme in the urine was determined.

2. The fat-splitting enzyme in the urine after ligation of the pancreatic ducts was determined.

3. The fate of the fat-splitting enzyme in the urine was determined when ligation of the pancreatic ducts was followed by pancreatectomy.

4. The excretion of the fat-splitting enzyme in the urine after removal of the pancreas was determined.

1. Methacholine and secretin * were employed in our experiments because these drugs are the most generally used stimulators of pancreatic secretion. Methacholine causes the concentration of the enzymes in pancreatic juice to rise without influencing the volume of the excreted juice. Injection of secretin increases the volume of the excreted pancreatic juice considerably, allowing the concentration of the enzymes even to fall, although not very much. Both drugs produce a marked rise of the total amount of enzymes present in the pancreatic juice.† The effect of methacholine and secretin on the excretion of the fat-splitting enzyme in the urine has been studied on normal dogs in about 50 experiments. We gave methacholine intramuscularly in quantities from 2.5 mg. to 10 mg., and we used secretin intravenously in amounts of 20 to 60 units. General reactions to secretin never occurred. Injection of methacholine in doses higher than 6 mg. often lead to strong salivation and diarrhea, depending on the weight of the dogs. We tried to avoid these incidents, not always with success, by keeping the dosage high enough to produce increased glandular function but not too high to spoil our experiments. The effect of methacholyl, given in increasing doses, on the excretion of fat-splitting enzyme in the urine is seen in Table 1.

TABLE 1.—*Effect of Methacholine on Excretion of Fat-Splitting Enzyme in Urine*

	Time	Fat-Splitting Enzyme/Cc. of Urine
6/10/53	Morning	0.35
6/11	Morning	0.3
6/12	Morning	0.25
6/17	10:00 a. m.	0.15
	11:00 a. m.	(4 mg. methacholine, i. m.)
	11:10 a. m.	0.35
	6:30 p. m.	1.05
6/18	Morning	0.55
	5:30 p. m.	0.2
6/19	Morning	0.25
6/19	10:30 a. m.	(6 mg. methacholine, i. m.)
	11:05 a. m.	0.7
	4:00 p. m.	0.4
6/20	Morning	2.15
	12:00 noon	0.5
	4:30 p. m.	0.55
6/21	Morning	0.05
	11:00 a. m.	0.1
6/23	Morning	0.5
	12:15 p. m.	(8 mg. methacholine, i. m.)
	12:30 p. m.	0.65
	6:30 p. m.	1.4
6/24	Morning	3.35
	12:00 noon	0.8
6/25	Morning	0.5
6/26	Morning	0.15

The concentration of the enzyme, less than 1.0 unit per cc. before each injection, rose to values between 1.05 and 3.35 in this experiment; in others, even as high as 6.4 after the injection of methacholine. The peak was usually reached in 10 to 18 hours. After 24 hours the effect was generally over. In a

* The secretin used in this study was given by Eli Lilly & Company, Indianapolis.

† References 5 and 6.

few experiments there was still a slight elevation of the values 24 hours after the injection.

The response of the fat-splitting enzyme in the urine to secretin was similar. The increase after secretin was often not quite so high, but it lasted longer. Table 2 illustrates the effect of secretin on the excretion of the fat-splitting enzyme.

TABLE 2.—*Effect of Secretin on the Excretion of Fat-Splitting Enzyme in Urine*

	Time	Fat-Splitting Enzyme/Cc. of Urine
6/29	Morning	0.55
6/29	6:00 p. m.	0.5
6/30	10:00 a. m.	0.25
	11:30 a. m.	40 units secretin i. v.
	12:15 p. m.	2.05
	4:30 p. m.	1.45
7/1	9:00 a. m.	1.3
	11:00 a. m.	60 units secretin i. v.
	1:15 p. m.	2.55
	6:30 p. m.	1.2
7/2	9:00 a. m.	1.1
	1:00 p. m.	1.05
7/3	Morning	1.35
	12:00 p. m.	0.35
7/6	Morning	0.35
7/7	Morning	0.35
	10:00 a. m.	Feeding
	11:00 a. m.	60 units secretin i. v.
	11:15 a. m.	0.9
	12:30 p. m.	1.3
7/8	8:00 a. m.	1.9
	10:00 a. m.	1.35
	6:00 p. m.	1.05
7/9	9:00 a. m.	0.65 no feeding
	11:00 a. m.	60 units secretin i. v.
	11:30 p. m.	0.55
	1:30 p. m.	1.10
7/10	9:00 a. m.	1.75
	11:00 a. m.	1.8 feeding
	3:00 p. m.	0.45
7/11	Morning	0.65

In this series of experiments, performed with the same dog as in the studies with methacholine, the concentration of the fat-splitting enzyme in the urine rose to 2.55; the effect lasted 30 to 36 hours. In another experiment, values of 0.65 and 0.75 before the injection rose to 4.05 in eight hours with 40 units of secretin. Twelve hours later the concentration of the fat-splitting enzyme was still 3.4. It sunk to between 0.1 and 0.45 on the third day. After a second injection of 40 units, the concentration rose again, this time to 4.9. Twenty-four hours after the injection, it was 3.45. Forty-eight hours after the injection, the concentration was 0.4, and 72 hours after the injection, 0.5.

Elevated figures of the enzyme in the urine are found for 36 to 48 hours after the injection of secretin. The quantity of urine collected in 24 hours after methacholine and secretin was never smaller but very often even larger than the amount of urine before the injection. Hence, methacholine and secretin produce an increased excretion of the fat-splitting enzyme in the urine and not only an increase in its concentration. Since methacholine and secretin increase the amount of lipase excreted from the pancreas into the duodenum, the conclusion is permitted, we believe, that the increased amounts of enzyme found in the urine are of pancreatic origin.

2. To further elucidate the relationship between the fat-splitting enzyme in the urine and the pancreas, we ligated the pancreatic ducts in dogs. We know from our own experiments on the effect of the ligation of the pancreatic ducts on serum lipase that it is almost invariably followed by a rapid rise of the serum lipase and that this rise is of relatively long duration. In the same way, a marked rise of the concentration of the fat-splitting enzyme in the urine occurs when the pancreatic ducts are ligated. Table 3 illustrates this effect on the concentration of the enzyme in the urine.

After five to six days, sometimes even a few days later, the concentration of the enzyme in the urine begins to fall. It reaches very low levels in 10 to 12 days. We never have seen it disappear completely in the periods we were able to observe our dogs.

When methacholine or secretin is given in the first days after the ligation of the ducts, very high values for the concentration of the enzyme in the urine may be reached. Table 4 shows this occurrence.

TABLE 3.—*Effect of Ligation of Pancreatic Ducts on Excretion of Fat-Splitting Enzyme in Urine*

	Time	Fat-Splitting Enzyme/Cc. of Urine
7/23	Morning	0.45
7/30	Morning	0.5
8/18	Morning	0.8 (serum lipase 0.35)
	Ligation of pancreatic ducts	
8/18	4:00 p. m.	0.05
8/19	Morning	1.35
8/20	4:00 p. m.	3.1
8/21	9:00 a. m.	1.85 (serum lipase 3.85)

3. In four dogs the ligation of the pancreatic ducts was followed by pancreatectomy, with the result that the fat-splitting activity in the urine disappeared after the second operation within 48 hours. There was no difference in the effect of the pancreatectomy whether the values for the fat-splitting enzyme in the urine were still high after the ligation of the ducts or had already fallen to low levels.

Table 5 illustrates the effect of ligation of the pancreatic ducts followed six days later

TABLE 4.—*Effect of Methacholine, Given Four Days After Ligation of Ducts, on Excretion of Fat-Splitting Enzyme in Urine (Same Dog as in Table 3)*

	Time	Fat-Splitting Enzyme/Cc. of Urine
8/18	Ligation performed	
8/22	Morning	2.1
	10:00 a. m.	(6 mg. methacholine i. m.)
	11:15 a. m.	2.8
	6:00 p. m.	6.4
8/23	Morning	1.8
8/25	Morning	1.2
8/28	Morning	0.2
8/30	Morning	0.2

by pancreatectomy on the concentration of the fat-splitting enzyme in the urine.

Injection of methacholine or secretin when given to pancreatectomized dogs had no effect on the excretion of the enzyme, in that no fat-splitting activity could be detected in the urine.

As Pratt and his co-workers [7] showed many years ago, tying the pancreatic ducts does not permanently exclude the pancreatic juice from the intestine. To accomplish this, it is necessary to place a barrier of living tissue in the form of the omentum between the duodenum and the pancreas. Otherwise the pancreatic juice about the tied ducts becomes activated, with the result that sinuses form that conduct the pancreatic juice into the intestine. With the pancreatic juice permanently excluded, rapid and extensive atrophy of the pancreas occurs. When this has taken place, injection of methacholine or secretin

TABLE 5.—*Excretion of Fat-Splitting Enzyme in Urine when Ligation of Ducts is Followed by Pancreatectomy*

	Time	Fat-Splitting Enzyme/Cc. of Urine
12/20	Morning	0.4
12/21	Morning	0.75
		Ligation of pancreatic ducts (urine not voided for 2 days)
12/23	Morning	0.45
12/24	Morning	2.35
12/25	Morning	2.5
12/26	Morning	1.4
	4:00 p. m.	2.95
12/27	Morning	1.45
	Pancreatectomy	
12/28	Morning	0
12/29	Morning	0.05
12/30	Morning	0.05

has almost no effect in increasing the fat-splitting enzyme in the urine.

4. In three dogs, extirpation of the pancreas was performed. The concentration of the fat-splitting enzyme in the urine started to decrease rapidly a few hours after the operation. The enzyme had disappeared com-

TABLE 6.—*Effect of Pancreatectomy on Excretion of Fat-Splitting Enzyme in Urine*

	Time	Fat-Splitting Enzyme/Cc. of Urine
5/6/54	Morning	0.25
5/10	Morning	0.6
5/12	Morning	0.4
5/12	Pancreatectomy	
5/13	Morning	0.3
5/14	Morning	0
5/15	Morning	0
5/16	Morning	0
5/17	Morning	0.05

pletely from the urine after 48 hours. The effect of total pancreatectomy on the fat-splitting enzyme in the urine is shown in Table 6.

In a patient with recurrent pancreatitis for whom subtotal pancreatectomy had been performed because of intractable pains and in two cases in which the pancreas had been removed because of a carcinoma of the biliary tract the concentration of the fat-splitting enzyme in the urine decreased gradually and was absent four to five days after the operation. We have seen one of the patients with carcinoma two years after his operation. He seemed to be in perfect health. There was apparently enough insular tissue left to prevent spontaneous glycosuria. No fat-splitting enzyme in the urine could be detected.

In one dog we succeeded in performing the complete series of experiments, including the examination of fat-splitting enzyme in the urine after injection of methacholine and secretin, after ligation of the pancreatic ducts, after ligation of the pancreatic ducts followed by injection of methacholine and secretin, and after ligation of the pancreatic ducts followed by pancreatectomy. Table 7 shows the result of this series of experiments.

TABLE 7.—*Series of Experiments on the Same Dog*

Time		Fat-Splitting Enzyme/Cc. of Urine
5/10/54	10:00 a. m.	0.45
5/11	10:00 a. m.	0.45
5/12	10:00 a. m.	0.35
	10:30 a. m.	4 mg. methacholine, i. m.
5/12	11:00 a. m.	0.4
	6:30 p. m.	1.9
5/13	8:00 a. m.	2.2
5/14	10:00 a. m.	0.8
5/16	10:00 a. m.	0.85
5/17	10:00 a. m.	0.3
5/18	10.00 a. m.	0.6
	10:45 a. m.	6 mg. methacholine, i. m.
	11:15 a. m.	0.7
	6:30 p. m.	5.35
5/19	8:00 a. m.	1.7
5/20	10:00 a. m.	0.05
5/21	Morning	0.3
5/22	Morning	0.45
	10:00 a. m.	40 units secretin
	Evening	1.4
5/23	Morning	1.9
5/23	Evening	1.3
5/24	Morning	0.3
6/14	Morning	0.4
	11:00 a. m.	60 units secretin
	12:00 noon	0.15
	4:00 p. m.	2.3
6/15	Morning	3.45
	5:00 p. m.	4.45
6/16	Morning	1.45
6/17	Morning	0.1
6/21	Morning	0.3
6/24	Morning	0.35
6/29	Morning	0.15
6/30	Ligation of pancreatic ducts	
7/2	Morning	1.5
7/7	Morning	3.1
	11:00 a. m.	8 mg. methacholine, i. m.
	11:45	3.0
	3:30 p. m.	2.7
	6:00	6.7
7/8	Morning	2.0
7/9	Morning	0.7
7/10	6:00 p. m.	1.35
7/12	Evening	1.1
7/13	9:00 a. m.	0.8
	11:00 a. m.	60 units secretin i. v.
	6:00 p. m.	0.4
7/14	Morning	0.1
7/15	Morning	0.35
7/18	Morning	0.05
7/19	Pancreatectomy	
7/20	Morning	0.7
	6:00 p. m.	0
7/21	9:00 a. m.	0.1
	10:00 a. m.	20 units insulin
7/22	8:00 a. m.	20 units insulin
	9:00 a. m.	0.1
	12:00 noon	0
	6:00 p. m.	0
7/23	Morning	0
	10:00 a. m.	8 mg. methacholine, i. m.
	12:00 noon	0
7/24	Morning	0.05
7/26	Morning	0
	11:00 a. m.	100 units secretin
	2:00 p. m.	0.05
7/27	Morning	0
7/27	Noon	0
7/28	Morning	0

The Table illustrates that in the same dog increasing amounts of methacholine and secretin produce an increased excretion of fat-splitting enzyme in the urine. The effect of secretin lasts at least 24 hours longer than the effect of methacholine. After ligation of the ducts the concentration of the enzyme in the urine rises and reaches the highest values

we have seen in our experiments after injection of methacholine. Injection of secretin two weeks after ligation had hardly any effect on the excretion of secretin. Two days after pancreatectomy, the fat-splitting enzyme in the urine had disappeared. Starting two days after removal of the pancreas, the dog is given 20 units of insulin daily. Insulin has no influence on the excretion of the enzyme. Methacholine injected four days after pancreatectomy and secretin given again three days later caused either no reappearance of the splitting enzyme in the urine or at most a mere trace.

Our experiments prove that (1) after injection of methacholine and secretin there is a markedly increased amount of fat-splitting enzyme detectable in the urine; (2) after ligation of the pancreatic ducts there is a marked rise in the excreted amount of the fat-splitting enzyme followed by a decrease to rather low levels; (3) after removal of the pancreas the fat-splitting enzyme disappears from the urine; (4) when the ligation of the ducts is followed by pancreatectomy the high values of fat-splitting enzyme in the urine decrease rapidly and no fat-splitting enzyme in the urine is detectable after two days.

From the data presented we believe the conclusion is warranted that the fat-splitting enzyme in the urine is of pancreatic origin and is identical with the pancreatic lipase. The first two series of experiments, i. e., the effect of injection of methacholine and secretin and the effect of ligation of the pancreatic ducts on the excretion of a fat-splitting enzyme in the urine, prove that these procedures are invariably followed by a rise of the concentration of the enzyme in the urine. These results, however, still do not justify the conclusion that the enzyme responsible for this rise has its origin in the pancreas. Other possibilities are to be considered. The pancreas may regulate the lipase level in the blood by excretion of any excess of the enzyme which is produced in some other organ. Ligation of the ducts would lead to an increase of the fat-splitting enzyme in the urine merely by removing this regulating factor. If the fat-splitting enzyme is derived from other sources than the pancreas and the pancreas is only the regulating factor, total removal of the gland will have the same effect as ligation of the ducts, elevation of the output of the enzyme. If, however, the fat-splitting enzyme in the urine is of pancreatic origin, it should disappear after total pancreatectomy. Since we were able to show in our Series 3 and 4 that the fat-splitting enzyme cannot be detected any more in the urine when total pancreatectomy was done alone or was carried out five to nine days after duct ligation, the pancreatic origin of this enzyme has been proved. The facts that the fat-splitting enzyme in the serum also rises after ligation of the pancreatic ducts, that it decreases after total pancreatectomy, and that it drops almost to zero when the duct ligation is followed by pancreatectomy [1] allow us to assume that the fat-splitting enzyme in the urine is identical with the serum lipase and the pancreatic lipase.

The figures for urinary lipase in our experiments have been expressed in units per cubic centimeter, which means as concentration of the enzyme in the urine. The elevation in the values for urinary lipase, however, is not only a rise of the concentration of the enzyme but it is a true increase of excreted lipase. Experiments performed to clear this question have shown us that injection of methacholine and secretin, as well as ligation of the pancreatic ducts, does not diminish the amount of urine. Often enough the excretion of urine is even increased.

The increase in urinary lipase does not correlate with the value of the lipase in the serum. An elevated serum lipase is not a prerequisite for an increase in urinary lipase. We have seen the rise of urinary lipase after ligation of the pancreatic ducts, when, according to an almost general agreement, there is an immediate increase of the lipase in the serum. But we have found the elevation of the values for urinary lipase also after injection of methacholine and secretin when, in contrast with the findings of some other investigators, we did not observe an

increase of blood lipase in a great number of such experiments.

SUMMARY

A method for the determination of a fat-splitting enzyme in the urine is described.

After injection of methacholine (Mecholyl) and secretin, the most generally used stimulators of pancreatic secretion, there is a markedly increased amount of fat-splitting enzyme detectable in the urine.

After ligation of the pancreatic ducts there is a marked rise in the excreted amount of the fat-splitting enzyme, followed slowly by a decrease to rather low values.

Pancreatectomy is followed by the disappearance of the fat-splitting enzyme from the urine.

When the ligation of the ducts is followed by pancreatectomy, the high values of fat-splitting enzyme disappear rapidly.

From the results of our investigations we conclude that the fat-splitting enzyme in the urine is of pancreatic origin and probably identical with the pancreatic lipase.

REFERENCES

1. Zorn, B.: Über fettspaltende Blut und Harnfermente und ihre Beziehungen zu physiologischen und pathologischen Vorgängen, Fermentforsch. **15**: 397, 1938.

2. Bockus, H. L., Editor: Postgraduate Gastroenterology as Presented in a Course Given Under the Sponsorship of the American College of Physicians in Philadelphia December MCMXLVIII, Philadelphia, W. B. Saunders Company, 1950, Vol. 3, p. 754.

3. Nothman, M. M.; Pratt, T. D., and Benotti, J.: The Effect of the Ligation of the Pancreatic Ducts and Pancreatectomy After Duct Ligation on Serum Lipase, J. Lab. & Clin. Med. **33**:833, 1948.

4. Peters, J. P., and VanSlyke, D. B.: Quantitative Clinical Chemistry: Vol. II. Methods, Baltimore, William & Wilkins Company, 1932, p. 816.

5. Agren, G., and Lagerlöf, H.: The Pancreatic Secretion in Man After Intravenous Administration of Secretin, Acta med. scandinav. **90**:1, 1936.

6. Comfort, M. W., and Osterberg, A. E.: Pancreatic Secretin in Man After Stimulation with Secretin and Acetyl-Beta-Methylcholine, Arch. Int. Med. **66**:688, 1940.

7. Pratt, G. H.; Lamson, P. D., and Marks, H. K.: The Effect of Excluding Pancreatic Juice from the Intestine, Tr. A. Am. Physicians **24**:266-281, 1909.

ASCHOFF BODIES IN LEFT AURICULAR APPENDAGES OF PATIENTS WITH MITRAL STENOSIS

Clinicopathologic Study, Including Postoperative Follow-Up

BENJAMIN MANCHESTER, M.D., Washington, D. C.
THOMAS M. SCOTTI, M.D., Coral Gables, Fla.
MARDELLE L. REYNOLDS, A.B.
and
WILHELMINA H. DAWSON, Washington, D. C.

IN RECENT years surgical valvulotomy for mitral stenosis has made it possible to examine microscopically the left auricular appendage and observe histologically the rheumatic process in a part of the heart during life. Since this is a phase in the natural history of rheumatic fever, it may be possible to correlate the incidence and degree of activity with the clinical events of rheumatic cardiac disease.

Although the lesions of rheumatic fever have been described in the left auricle proper,* the auricular appendage has escaped more critical examination. Von Glahn,[8] in a study of rheumatic auricular endocarditis, concluded that the changes observed may extend into the first portion of the auricular appendage. He did not, however, record Aschoff bodies in this location. Similarly, Gross,[9] in an exhaustive review of rheumatic auricular lesions, made no reference to the auricular appendage.

Unusual circumstances have on occasion prompted the making of sections of this site. Graef, Berger, Bunim, and de la Chapelle [10] described evidences of rheumatic activity beneath thrombi in the appendages in 7 of 10 cases. In a control series of 30 rheumatic hearts without thrombi, sections of appendages were not available. The significance of such rheumatic activity was pursued to the conclusion that it predisposed to auricular thrombus formation.

Recent reports † indicate that the rheumatic lesion, the Aschoff body found everywhere in the heart, is also noted in the auricular appendage. The principal objective of this study is to investigate the possible relationship between the morphologic changes and the clinical features of rheumatic disease.

MATERIALS AND METHODS

Observations were made on the tips of the left auricular appendages removed at operation for mitral valvulotomy in 35 patients. The material examined consisted of microscopic sections which were contributed to the Armed Forces Institute of Pathology by pathologists of various Armed Forces and Veterans Administration Hospital laboratories. In general, the microscopic sections as received were sufficient for the study. In some instances additional sections were prepared at the AFIP from the paraffin blocks and/or fixed tissues also submitted by the contributors. Hematoxylin-and-eosin-stained sections only were examined. In each case the clinical records were obtained and reviewed, and in the 33 cases in which the patients survived the operation, follow-up information was requested from them or their physicians. In two instances the patient died shortly after the operation and material obtained at autopsy was available for study.

As control material, autopsy specimens of hearts from 57 cases in the files of the AFIP were examined. The tip of the left auricular appendage corresponding to the amount of tissue generally removed at operation was obtained from these hearts, both "normal" and diseased. The specimens were examined microscopically in the routine manner usually at three, but sometimes at two, levels. The "normal" hearts were those of men killed in battle who had no primary heart disease, although incidental coronary atherosclerosis of varying degree was present in some. The hearts of the "old rheumatic carditis" group were those of patients

From the Armed Forces Institute of Pathology and the Department of Medicine, George Washington University School of Medicine, Washington, D. C., Assistant Clinical Professor of Medicine, George Washington University School of Medicine (Dr. Manchester) and Associate Professor of Pathology, University of Miami School of Medicine (Dr. Scotti).

* References 1-7.

† References 11-20.

in whom the disease was considered clinically inactive. The specimens examined were as follows:

Diagnosis		Specimens, No.
"Normal"		25
Old rheumatic carditis		12
Mitral stenosis	5	
Calcified aortic stenosis	3	
Valvulitis with subacute bacterial endocarditis	4	
Other diseased hearts		20
Myocardial infarct	7	
Syphilitic heart disease	3	
Neoplasms	3	
Pericarditis	2	
Trauma	1	
Periarteritis nodosa	1	
Dissecting aneurysm aorta	1	
Adult endocardial sclerosis	1	
Hypertensive heart disease	1	

Cases of clinically active rheumatic carditis were not included in the control group, since gross heart specimens of such cases were not available at the time of this study nor were there any microscopic sections of the auricular appendages of these cases in the files.

PATHOLOGIC FINDINGS

The changes observed microscopically in the specimens of the study group and control group are listed in Table 1.

Aschoff bodies were noted in 13 of the 35 cases (37.14%) of the study group. These lesions were graded quantitatively 1+ to 4+, and in each instance they were present in the subendocardial region. In only four cases were Aschoff bodies found in the myocardium as well.

The lesion identified as an Aschoff body consisted of a focal accumulation of histiocytes interstitially, associated with swollen eosinophilic fragmented collagen. Among the histiocytes were cells with abundant somewhat basophilic cytoplasm and a nucleus with

TABLE 1.—*Summary of Pathologic Findings in Study and Control Cases*

	Biopsy Study Cases			Control Autopsy Cases			
				Old Rheumatic Carditis			
Pathologic Findings	All Cases (35 Cases)	With Aschoff Bodies (13 Cases)	Without Aschoff Bodies (22 Cases)	Mitral Stenosis (5 Cases)	Other (7 Cases)	Other Diseased Hearts (20 Cases)	"Normal" (25 Cases)
Subendocardium							
Aschoff bodies	13	13*	0	2†	0	0	0
Nonspecific inflammation	17	8	9	2	4	0	1
Fibrosis	15	6	9	2	3	7	3
Myocardium							
Aschoff bodies	4	4‡	0	0	0	0	0
Nonspecific inflammation	10	5	5	3	5	1	1
Fibrosis	17	7	10	1	1	2	1
Hypertrophy	16	8	8	3	0	2	0
Epicardium							
Nonspecific inflammation	27	11	16	5	5	15	6
Fibrosis	18	8	10	3	0	10	3

* Quantitatively, the Aschoff bodies in the subendocardium were 1+, one case; 2+, 3 cases; 3+, 1 case; 4+, 3 cases.
† Quantitatively, the Aschoff bodies in the subendocardium were 1+ in each case.
‡ Quantitatively, the Aschoff bodies in the myocardium were 1+ in each case.

TABLE 2.—*Nonspecific Inflammation in Study and Control Cases*

		Nonspecific Inflammation		
	Aschoff Bodies	Subendocardium	Myocardium	Epicardium
Study group	Aschoff bodies in subendocardium only (9 cases)	4	4	8
	Aschoff bodies in subendocardium and myocardium (4 cases)	3	1	3
	No Aschoff bodies (22 cases)	9	5	16
Rheumatic carditis control group	Mitral stenosis with Aschoff bodies in subendocardium (2 cases)	2	2	2
	Mitral stenosis with no Aschoff bodies (3 cases)	0	0	2
	Others (7 cases), no Aschoff bodies	6	6	6
Other diseased hearts control group	No Aschoff bodies (20 cases)	0	1	15
"Normals"	No Aschoff bodies (25 cases)	1	1	6

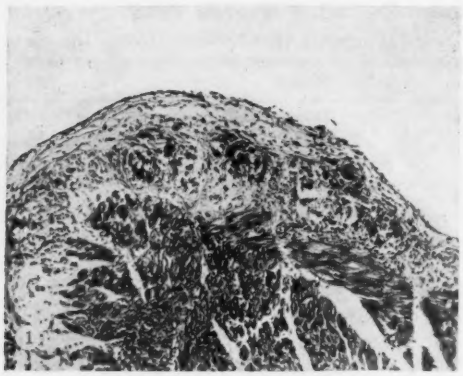
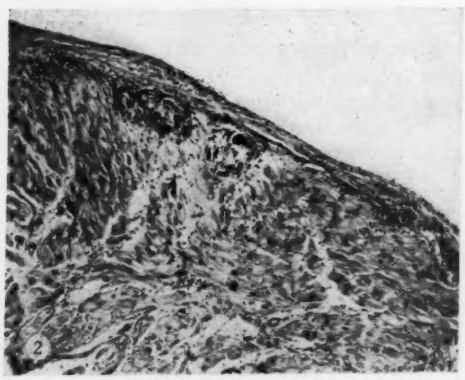


Fig. 1.—Aschoff bodies in subendocardium, left auricular appendage, associated with nonspecific inflammation. AFIP Acc. No. 542928, Neg. No. 53-14064.

a distinct nuclear membrane and a large nucleolus, i. e., Aschoff cells. Some of these cells were multinucleated.

As indicated in Table 2, a nonspecific inflammatory reaction was observed both in sections showing Aschoff bodies and in those without Aschoff bodies. The reaction consisted chiefly of lymphocytes and histiocytes and occasionally neutrophiles. In one instance there was marked infiltration by eosinophiles throughout all layers of the auricular appendage, together with Aschoff bodies in the subendocardium. This was in a patient who had a rather high blood eosinophilia of undetermined cause.

Fig. 2.—Subendocardial Aschoff bodies, associated with nonspecific inflammation, encroaching upon myocardium. AFIP Acc. No. 542928, Neg. No. 53-1689-1; reduced approx. 44% from mag. × 90.



In the subendocardium and myocardium the nonspecific inflammatory reaction was observed as focal accumulations or as cells scattered throughout the interstitial tissue, and in sections showing Aschoff bodies these cells were intermingled with the components of the Aschoff body. In three cases of the group not showing Aschoff bodies in sections of the auricular appendages, the nonspecific inflammatory reaction in the subendocardium consisted of foci of small histiocytes with darkly stained nuclei associated with slight fragmentation of the collagen. These lesions suggested Aschoff bodies, but, because of the absence of characteristic Aschoff cells and the lack of more definite collagen change, they were not interpreted as

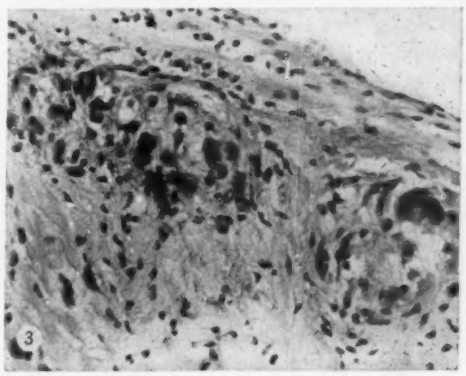


Fig. 3.—High-power view of lesions seen in Fig. 2, illustrating details of Aschoff bodies, including multinucleated Aschoff cells. AFIP Acc. No. 542928, Neg. No. 53-1688-8; reduced approx. 44% from mag. × 282.

such. In another instance a similar focus was observed in the interstitial tissue of the myocardium, but for the same reasons it was not regarded as an Aschoff body. The nonspecific inflammation in the epicardium usually consisted of foci of lymphocytes, often associated with small areas of fibrosis. Occasionally a small number of lymphocytes and neutrophiles were scattered throughout the epicardium. No Aschoff bodies were found in the epicardium in any of the cases.

In the sections of auricular appendages of the two patients who died postoperatively there were no Aschoff bodies, nor were any Aschoff lesions observed in sections of heart

obtained at autopsy. One heart, however, showed rather pronounced nonspecific myocarditis, and another, focal perivascular fibrosis of the myocardium and fibrinous pericarditis.

Aschoff bodies were observed in only two cases of the control group, in both instances in the subendocardium of hearts showing old rheumatic carditis with mitral stenosis. The lesions were not as striking as those noted in the auricular appendages removed at operation. An Aschoff body was found also in the myocardium of one of the routine sections of heart obtained at autopsy in one of these cases. Nonspecific inflammation was noted rather frequently in all layers of the auricular appendages of the "old rheumatic carditis" control group and in the epicardium of the appendages of the other cases of the control group, but it was not a common finding in the subendocardium and myocardium of the latter cases.

CLINICAL FINDINGS

Available data in case folders and clinical records were analyzed for symptoms, signs, and laboratory-test results that would represent the features of rheumatic activity. Follow-up data were obtained for comparison and prognosis of patients with positive and negative biopsies.

The study of available clinical and laboratory data was limited by the lack of detailed information concerning past history. However, there appeared to be no clinical differences between the 13 patients with positive and the 22 with negative biopsy findings.

Fifteen of the patients were females; biopsy was positive in only 3 of these, as compared with 10 of the 20 males. However, a χ-square test failed to demonstrate a relationship between Aschoff bodies and sex of the patients.

An earlier diagnosis of rheumatic heart disease in females is indicated by the fact that this diagnosis was not made for any male before the age of 15, while it was made for one-third of the females before that age (Table 3). Also, there are indications that rheumatic fever was acquired or diagnosed earlier in the females, but ages at time of this diagnosis were reported by only eight male and six female patients. Three other females had definite diagnosis of rheumatic fever in childhood, but the remainder of 18 patients denied a history of rheumatic fever. Since the median ages at time of operation were approximately equal for males and females, 32.5 and 33.2 years, respectively, and those at diagnosis of rheumatic heart disease were younger for females, it is apparent that the average interval between this diagnosis and operation was longer for female than for male patients. The average intervals were 12.3 and 6.9 years, respectively (Table 4).

TABLE 3.—*Ages of Male and Female Patients at First Diagnosis of Rheumatic Heart Disease*

Age Group	Number			%		
	Total	Male	Female	Total	Male	Female
All ages	35	20	15	100	100	99
6-15	5	..	5	14	...	33
16-25	17	12	5	49	60	33
26-35	9	6	3	26	30	20
36-45	3	1	2	8	5	13
Over 45	1	1	..	3	5	..

The age distribution of the 35 patients at the time of mitral valvulotomy is shown in Table 5. The average age at operation of patients with positive biopsies (28.9 years) was significantly younger than that of the patients whose biopsies were negative (36.0 years). The only positive biopsy in a patient over 40 years of age was in a 43-year-old woman, for whom the first diagnosis of rheumatic heart disease was made at the age of 13.

Although the biopsy was positive in 5 of the 12 patients with a history of arthritis and in 3 of 6 who had chorea, χ-square tests indicated that the patients in the group with positive biopsies were no more likely to have

TABLE 4.—*Interval from First Diagnosis of Rheumatic Heart Disease to Operation*

Interval, Yr.	Total	Male	Female
Total	35	20	15
Less than 1	3	3	..
1-4	7	4	3
5-9	16	10	6
10-14	3	2	1
15-19	2	..	2
20-24	1	..	1
25-29	2	1	1
30	1	..	1
Av. interval	..	6.9	12.3

TABLE 5.—*Ages of Patients at Time of Mitral Valvulotomy*

Age, Yr.	Total	Patients, No.	
		With Aschoff Bodies	With No Aschoff Bodies
Total	35	13	22
18	1	..	1
19	1	1	..
21	1	..	1
24	2	1	1
25	1	..	1
26	2	1	1
27	2	2	..
28	1	1	..
29	5	4	1
31	1	1	..
32	2	..	2
34	3	..	3
35	3	1	2
36	2	..	2
43	2	1	1
46	2	..	2
47	1	..	1
52	2	..	2
55	1	..	1
Av. age	..	28.9	36.0

had either of these disease conditions than were those with negative biopsies (Table 6).

The major signs and symptoms noted at the time of admission for mitral valvulotomy were exertional dyspnea in all 35 patients; hemoptysis, orthopnea, or both in 19; paroxysmal nocturnal dyspnea in 14, and cough in 12.

Digitalis had been administered to 28 patients prior to admission. In this group there were nine patients with Aschoff bodies in the subendocardium, including one with these bodies also in the myocardium. Three additional patients received digitalis at the time they were admitted for operation; Aschoff bodies were found in both the subendocardium and the myocardium in two. Biopsies were positive in two of the remaining four patients without heart failure who had not had digitalis; in one of these, Aschoff bodies were found in both subendocardium and myocardium.

TABLE 6.—*Associated Conditions Referable to Rheumatic Fever*

Associated Conditions	Cases, No.
Not stated	2
None *	9
Chorea	3
Arthritis	7
Tonsillitis	4
Epistaxis	1
Unexplained fever	2
Chorea and arthritis	1
Chorea and scarlet fever	1
Chorea, arthritis and scarlet fever	1
Arthritis and tonsillitis	1
Arthritis and epistaxis	1
Arthritis and scarlet fever	1
Epistaxis and scarlet fever	1
Total	35

* One patient with a history of "catarrhal fever" had none of the usual conditions associated with rheumatic fever.

No statistical relationship could be demonstrated between the duration of heart failure and the presence or absence of Aschoff bodies or the quantitative grading of these bodies (Tables 7 and 8).

The size of the heart as determined by physical, x-ray, and fluoroscopic examinations could not be related to the presence of Aschoff bodies. Cardiac involvement was moderate or marked in 12 of the 13 patients with positive and 20 of the 22 with negative biopsies. Auricular fibrillation was noted but once in the 13 cases with positive biopsies, while 12 of the 29 patients with normal sinus rhythm at the time of admission had positive biopsies. Although the six patients with auricular fibrillation at time of admission had all experienced episodes of heart failure within four months of operation, biopsy was positive for Aschoff bodies in only one. Thirteen others in heart failure within the same period had negative biopsies and no auricular fibrillation.

Auriculoventricular conduction disturbance, manifested by prolonged P-R interval, was observed in 3 of the 13 in the group with positive biopsies and in none of the 22 in the group with negative biopsies. Two of the 3 patients with a prolonged P-R interval and 8 of the 10 in the positive biopsy group with normal A-V conduction received digitalis. It is improbable that digitalis contributed to the prolonged P-R interval.

The white blood cell count at the time of operation was normal in 20 patients, 7 of whom had positive biopsies; it was increased in 12, of whom 4 had Aschoff bodies.

The erythrocyte sedimentation rate at operation was recorded for 25 patients. The rates were abnormal in 5 of the 10 with Aschoff bodies and in 6 of the 15 who had no Aschoff bodies on pathologic examination. None of the 11 patients with abnormally high

sedimentation rates had fever at time of operation.

One of the 11 patients with abnormal sedimentation rates at time of operation died 24 hours after attempted mitral valvulotomy. However, this patient, a white man 52 years of age, had previously been judged an unsuitable candidate for surgery by the criteria then extant. His condition steadily declined in spite of all therapeutic measures. No Aschoff bodies were found in the auricular appendage.

Two additional patients, for whom the sedimentation rates at time of operation were not recorded, had preoperative sedimentation rates ranging from normal to high. One of these, a 29-year-old white man with positive biopsy, had two episodes of heart failure three months postoperatively, and at last report, 23 months after operation, there was no evidence of improvement. The other patient, also a 29-year-old white man, whose biopsy was negative, was in heart failure when admitted for operation. He died four days after attempted mitral valvulotomy.

Eosinophiles were found in the auricular appendage of one patient whose preoperative blood cell counts were within normal limits. The patient had undergone cardiac catheterization two weeks previously; on the day following mitral valvulotomy the eosinophile count rose to 3%; one week later it was 34%. Histologic examination indicated inflammatory reactions of two types in the section of the left auricle; nodular accumulation of Aschoff cells in the subendocardial region, associated with changes in the collagen, and a more acute reaction, consisting of edema; dilatation of vessels; infiltration by granulocytes, neutrophilic and eosinophilic, and margination. Recovery was uneventful, and follow-up information submitted by her physician 16 months later noted increased exercise tolerance, with no episodes of heart failure, auricular fibrillation, or rheumatic reactivation. She recovered without complication from appendectomy performed five months after the mitral valvulotomy.

An attempt to correlate the positive histologic findings with the date of operation failed to reveal any seasonal variation of the Aschoff lesion. Nineteen, or 54%, of the patients had mitral valvulotomies during December through February; the biopsies were positive in only six of these.

The immediate postoperative course, i. e., the hospital course, was completely unevent-

TABLE 7.—*Digitalization and Cardiac Failure in Patients With and Without Aschoff Bodies*

Digitalization and Interval from Cardiac Failure to Operation	Number			%		
	Total	With Aschoff Bodies	Without Aschoff Bodies	Total	With Aschoff Bodies	Without Aschoff Bodies
Digitalis						
Failure within 6 mo.	23	8	15	100	35	65
Failure 7-24 mo.	8	3	5	100	37	63
No digitalis						
No evidence of failure	4	2	2	100	50	50

TABLE 8.—*Relation of Aschoff Bodies to Clinical Data*

Grade of Aschoff Bodies	Total	Digitalis Within 2 Yr. of Operation	Enlarged Heart by X-Ray	Auricular Fibrillation	A-V Conduction Disturbance	Abnormal Sed. Rates	Increased WBC	Prob. Rheum. Reactivation Postoperatively
Aschoff bodies								
1+	4	4	4	1	2	3	1	..
2+	5	3	5	..	..	2	1	3
3+	1	1	..	..	..	..	..	..
4+	3	3	3	..	1	..	2	1
Total	13	11	12	1	3	5	4	4
No Aschoff bodies	22	20	20	5	..	6	8	8
Total	35	31	32	6	3	11	12	12

ful for 5 (38%) of the 13 patients with and 9 (41%) of the 22 without Aschoff bodies.

The characteristic features of probable rheumatic reactivation were protracted convalescence, low-grade fever, the persistence of pleural and pericardial friction rub beyond the usual postoperative period, and arthralgias. Suspected postoperative rheumatic reactivation occurred in 4 of the 13 patients with positive biopsies (31%) and in 8 of the 22 with negative biopsies (36%). Statistical tests indicate no greater likelihood of recurrence of rheumatic activity in the first group than in the second. These results are in accord with the observations reported by Soloff and associates.[21]

Thirty-two patients (91.4%) in the present study experienced improvement after mitral valvulotomy, as compared with their preoperative condition. In the three remaining patients the operation was performed as the only therapeutic measure which might possibly improve the condition.

Twenty-four patients, including 9 with positive biopsies, have now been followed from 12 to 29 months (average, 19 months). Seventeen of these had episodes of cardiac failure, auricular fibrillation, or probable rheumatic reactivation during the 12 months after operation. However, in only four was auricular fibrillation reported and two others were known to be receiving digitalis at last follow-up. Only two of these six had Aschoff bodies in the auricular appendage at time of operation. The condition of all but 1 of the 24 is greatly improved when compared to that during the preoperative period. It would appear that the clinical course following mitral valvulotomy may be as favorable for patients with histologic but not clinical evidence of rheumatic activity as for those with neither clinical nor pathologic evidence (Table 9).

TABLE 9.—*Incidence of Specific Disease Conditions Following Mitral Valvulotomy**

Disease Condition	Total	Interval to Last Known Status: Under 12 Mo. — Aschoff Bodies	Under 12 Mo. — No Aschoff Bodies	12-29 Mo. — Aschoff Bodies	12-29 Mo. — No Aschoff Bodies
Total patients	33†	4	5	9	15
Cardiac failure	7	..	..	3	4
Auricular fibrillation	14	2	2	3	7
Probable rheumatic reactivation	12	1	1	3	7
None or not stated	10	1	2	4	3

* No patients reported fever or joint pains at time of last follow-up; four reported auricular fibrillation, and two stated that they were receiving digitalis.

† Two patients who died within four days after operation are omitted from the table.

COMMENT

The present report confirms the observations well known to clinicians and pathologists that active rheumatic carditis may be present even when clinical and laboratory methods fail to indicate much activity. The statistical evaluation of the present series of 35 patients did not produce any significant diagnostic criteria. However, some of the usual clinical signs regarded as possible manifestations of subclinical rheumatic activity were inadequate for evaluation.

The relation between the rheumatic inflammatory process and the left auricular appendage as a strategic site representative of the rheumatic lesions in the ventricular myocardium, valve rings, valve substance, and pericardium has not been established. The observations of Thomas and co-workers,[19] Decker and co-workers,[18] Kuschner and Levieff,[23] and McKeown [22] suggest that the left auricular appendage is not a favored site for the development of Aschoff bodies.

Thomas and co-workers [19] reported that in an autopsy series of 29 hearts with Aschoff bodies in the left auricular appendage 25 (85%) also showed similar lesions in routine sections from other portions of the heart. In the same series lesions were present in routine autopsy sections in 8 of the 11 cases (73%) when no Aschoff lesions were noted in the appendage. Kuschner and Levieff,[23] who studied the hearts in 40 cases of rheumatic heart

disease, observed Aschoff bodies in the ventricular myocardium in 8 of 9 cases with lesions in the left auricular appendage. Also, in six cases in which Aschoff bodies were not seen in the appendages the lesions were found in the ventricular myocardium in two. Decker and co-workers,[18] who observed Aschoff bodies in 83 (45.3%) of 183 auricular biopsies, studied 22 cases which came to autopsy. Aschoff bodies were present in the auricular appendages in five of these cases; in four of these, lesions were found in the ventricular myocardium also. In a sixth case, lesions were not found in the auricular appendage but were seen elsewhere in the heart. In the control material, 11 hearts showing unequivocal stigmata of rheumatic heart disease were examined. In two of them Aschoff bodies were found in both the left auricular appendage and the left ventricular myocardium. In the report by McKeown,[22] 24 of 53 auricular appendages removed surgically showed lesions which were interpreted as Aschoff nodules. The report also includes a study of 92 cases of mitral stenosis at autopsy. Sections of the auricular appendage and left ventricle were examined.

Aschoff bodies were found in both the appendages and the myocardium of the left ventricle in 17 of these cases and in the left ventricle only in 5.

Microscopic evidence of rheumatic activity is often an incidental finding, the frequency depending on the criteria employed.[24] Evidence of active rheumatic carditis (as high as 32%) has been reported in subjects in the fifth to eighth decades of life.‡

In the series of resected auricular appendages presented here the frequent occurrence of Aschoff bodies (37%) in the absence of rheumatic activity clinically may be compared to what has been noted in other reports in which the incidence of Aschoff bodies or "lesions resembling Aschoff bodies" was also high (25 to 74%).§

Enticknap,[17] who described the lesions in his group of cases as "probable" or "possible" Aschoff bodies, raised a doubt as to whether he was dealing with true Aschoff bodies. He suggested "that the best course is to regard the appearances seen as a new finding, the significance of which can only be elucidated by prolonged clinical-pathological investigation of, in particular, the subsequent progress of the disease and morbid-anatomical changes in the hearts in which they were found."

In our study, a lesion was regarded as an Aschoff body when it consisted of a focal accumulation, interstitially, of histiocytes including characteristic single or multinucleated Aschoff cells, associated with swollen, eosinophilic, frequently fragmented collagen. Foci of histiocytes without the characteristic collagen change and Aschoff cells suggested Aschoff bodies but were not regarded as such.

Supporting evidence that the lesions observed in the present series are Aschoff bodies may be seen in the study by Thomas and co-workers.[19] Lesions found in auricular appendages surgically removed were compared with those observed in appendages obtained from heart specimens of patients who died with fulminating rheumatic fever. In the surgical group 55% showed Aschoff bodies in the endocardium, and in the autopsy series, 72%. The lesions in one group were indistinguishable from those in the other.

It is the impression of the authors that the lesions regarded as Aschoff bodies in this study are indicative of active rheumatic heart disease, despite the fact that the disease was considered inactive clinically. The possibility was entertained that the lesions may represent Aschoff-like granulomas, which occur in certain hypersensitivity states other than rheumatic fever, but there was no evidence to this effect except in the one patient with high blood eosinophilia of doubtful origin and pronounced eosinophilic infiltration of the auricular appendage.

The significance of the nonspecific inflammation is difficult to evaluate. It is well known that in active rheumatic heart disease a nonspecific inflammatory reaction accompanies the specific lesions, occurring not only in the vicinity of the Aschoff bodies but elsewhere

‡ References 25-28.

§ References 11-20.

in the heart as well. It is possible, therefore, that the nonspecific inflammation seen in the cases of the study group (excluding the acute reaction which might have resulted from operative trauma) represents, at least in part, the residual nonspecific inflammatory component of rheumatic carditis. The findings as noted in Tables 1 and 2 seem to suggest this, at least as far as the reaction in the subendocardium and myocardium is concerned. Nonspecific inflammation occurred very frequently in these regions, not only in the series studied but also in the "old rheumatic carditis" control group, and only in an occasional instance in the nonrheumatic controls. It does not appear that this inflammation is related to organizing auricular thrombi, for the latter were noted in only two cases, one in the study group and one in the "old rheumatic carditis" control group, both without Aschoff bodies. As for the nonspecific reaction in the epicardium, it cannot be attributed to previous rheumatic heart disease, since it also occurred rather frequently in the nonrheumatic control cases.

Some results of an attempt to relate rheumatic activity to the more prominent clinical signs and symptoms are worthy of note. The prevailing opinion that heart failure in the first four decades of life in persons with rheumatic valve disease is due, in the majority of instances, to active rheumatic carditis was not confirmed in this study.[29] Of 31 patients with congestive heart failure, only 11 (35.5%) showed rheumatic activity. Cardiac enlargement due either to dilatation or to hypertrophy likewise failed to serve as a significant clinical index of rheumatic activity.

Auricular fibrillation is seldom seen during rheumatic activity. When it is present, it is usually the result of the hemodynamic alterations associated with long-standing mitral stenosis. It may serve as an index of the severity and high degree of mitral valve disease; hence it is an arrhythmia that is usually a late sign of long-standing rheumatic heart disease.‖ In the present series only one of six patients with auricular fibrillation showed Aschoff bodies. This relationship of auricular fibrillation with the low incidence of Aschoff bodies has been observed by NcNeely and his associates.[20]

The electrocardiogram, as a rule, is of little value in indicating rheumatic activity in the later years of the disease. A prolonged P-R interval, however, may be due to active rheumatic carditis. In the three patients with prolonged P-R interval, Aschoff bodies were noted; two of these had been given digitalis. In the other 10, patients with positive biopsies, the P-R interval was normal, and 8 had received digitalis. While the significance of this cannot be fully evaluated, it does not seem probable that digitalis was responsible for this conduction disturbance.

The presence or absence of Aschoff bodies in the resected auricular appendages of patients without clinical evidence of rheumatic activity was of little prognostic importance. The postoperative course indicated that patients with Aschoff bodies in this site did as well as those who did not show stigmata of active rheumatic carditis. The postoperative reactivation of rheumatic fever was no more frequent from a statistical standpoint among those without Aschoff bodies than in the group with positive biopsies.

The limitations of clinical and laboratory methods in the detection of active rheumatic carditis are reflected in the present report. The discrepancy between the clinical features and the histologic evidence of rheumatic activity is advantageous to the patient, but it is less fortunate for those investigators interested in the problem of rheumatic heart disease, who find it difficult to reconcile the differences.

SUMMARY

The records of 35 patients operated upon for mitral stenosis have been reviewed. The biopsy specimens of the left auricular appendages were examined, and Aschoff bodies were noted in 13 (37%). Clinical and laboratory methods are inadequate for the detection of active subclinical rheumatic carditis. The postoperative mortality and morbidity, as well as clinical improvement, were the same for the group of cases in which biopsy was positive

‖ References 30 and 31.

for Aschoff bodies and the group in which it was negative. Probable reactivation of rheumatic fever occurred with equal frequency, statistically, in the two groups.

REFERENCES

1. Corvisart, J. N.: Essai sur les maladies et les lésions organiques du cœur et des gros vaisseaux, Paris, Migneret, 1806.

2. Burns, A.: Observations on Some of the Most Frequent and Important Diseases of the Heart, Edinburgh, J. Muirhead, 1809, Chap. 9.

3. Baillie, M.: The Morbid Anatomy of Some of the Most Important Parts of the Human Body, Ed. 5., London, W. Bulmer & Company, 1818.

4. Wells, W. C.: On Rheumatism of the Heart, Tr. Soc. Improve. M. & Chir. Knowl. **3**:373-424, 1812.

5. Laennec, R. T. H.: De l'auscultation médiate, ou traité du diagnostic des maladies des poumons et du cœur, fondé principalement sur ce nouveau moyen d'exploration, Paris, J. A. Brosson and J. S. Chaudé, 1819, Vol. 2, p. 127.

6. Hope, J.: Treatise on Diseases of the Heart and Great Vessels, London, William Kidd, 1832, p. 149.

7. Bouillaud, J.: Traité clinique des maladies du cœur, Paris, J. B. Baillière, 1835, Vol. 2, p. 28.

8. Von Glahn, W. C.: Auricular Endocarditis of Rheumatic Origin, Am. J. Path. **2**:1-14, 1926.

9. Gross, L.: Lesions of the Left Auricle in Rheumatic Fever, Am. J. Path. **11**:711-735, 1935.

10. Graef, I.; Berger, A. R.; Bunim, J. J., and de la Chapelle, C. E.: Auricular Thrombosis in Rheumatic Heart Disease, Arch. Path. **24**:344-365, 1937.

11. Pinniger, J. L.: The Left Auricular Appendage in Mitral Stenosis: Study of 15 Cases Submitted to Valvulotomy, St. Thomas's Rep. **7**:54-62, 1951.

12. Kuschner, M.; Ferrer, M. I.; Harvey, R. M., and Wylie, R. H.: Rheumatic Carditis in Surgically Removed Auricular Appendages, Am. Heart J. **43**:286-292, 1952.

13. Sabiston, D. C., Jr., and Follis, R. H., Jr.: Lesions in Auricular Appendages Removed at Operations for Mitral Stenosis of Presumed Rheumatic Origin, Bull. Johns Hopkins Hosp. **91**:178-187, 1952.

14. Ellis, L. B., and others: Studies in Mitral Stenosis: Correlation of Physiologic and Clinical Findings, A. M. A. Arch. Int. Med. **88**:515-531, 1951.

15. Biorck, G.; Winblad, S., and Wulff, H. B.: Studies in Mitral Stenosis: II. Observations on Incidence of Active Rheumatic Carditis in Left Auricular Appendages Resected at Operation for Mitral Stenosis, Am. Heart J. **44**:325-332, 1952.

16. Janton, O. H., and others: Results of Surgical Treatment for Mitral Stenosis: Analysis of 100 Consecutive Cases, Circulation **6**:321-333, 1952.

17. Enticknap, J. B.: Biopsy of the Left Auricle in Mitral Stenosis, Brit. Heart J. **15**:37-46, 1953.

18. Decker, J. P.; Hawn, C. Van Z., and Robbins, S. L.: Rheumatic "Activity" as Judged by the Presence of Aschoff Bodies in Auricular Appendages of Patients with Mitral Stenosis: I. Anatomic Aspects, Circulation **8**:161-169, 1953.

19. Thomas, W. A.; Averill, J. H.; Castleman, B., and Bland, E. F.: The Significance of Aschoff Bodies in the Left Atrial Appendage, New England J. Med. **249**:761-765, 1953.

20. McNeely, W. F.; Ellis, L. B., and Harken, D. E.: Rheumatic "Activity" as Judged by the Presence of Aschoff Bodies in Auricular Appendages of Patients with Mitral Stenosis: II. Clinical Aspects, Circulation **8**:337-344, 1953.

21. Soloff, L. A., and others: Reactivation of Rheumatic Fever Following Mitral Commissurotomy, Circulation **8**:481-497, 1953.

22. McKeown, F.: Left Auricular Appendage in Mitral Stenosis, Brit. Heart J. **15**:433-438, 1953.

23. Kuschner, M., and Levieff, L.: Correlation Between Active Rheumatic Lesions in the Left Auricular Appendage and Elsewhere in the Heart, Am. J. M. Sc. **226**:290-295, 1953.

24. Hall, E. M., and Anderson, L. R: The Incidence of Rheumatic Stigmas in Hearts Which Are Usually Considered Nonrheumatic, Am. Heart J. **25**:64-80, 1943.

25. Rothschild, M. A.; Kugel, M. A., and Gross, L.: The Incidence and Significance of Active Infection in Cases of Rheumatic Cardiovascular Disease During the Various Age Periods, Am. Heart J. **9**:586-595, 1934.

26. Kaufman, P., and Poliakoff, H.: Studies on the Aging Heart: I. The Pattern of Rheumatic Heart Disease in Old Age (A Clinical-Pathological Study), Ann. Int. Med. **32**:889-904, 1950.

27. Wroblewski, F., and Messinger, W. J.: Active Rheumatic Carditis in Patient over 40 Years of Age, Am. Heart J. **40**:345-353, 1950.

28. Appel, S. B., and Kossmann, C. E.: Rheumatic Heart Disease in Patients over 60 Years of Age, J. A. M. A. **146**:1474-1478, 1951.

29. Wilson, G.: Rheumatic Fever, New York, The Commonwealth Fund, 1940, p. 266.

30. Cookson, H.: Mitral Stenosis in Later Life, Brit. Heart J. **11**:155-164, 1949.

31. Kossmann, C. E., and Connor, C. A. R.: Auricular Fibrillation of Long Duration in Rheumatic Heart Disease, Am. Heart J. **24**:215-222, 1942.

CARBOHYDRATE METABOLISM IN BRAIN DISEASE

IV. Effect of Hydrocortisone and Corticotropin (ACTH) on the Metabolic Effects of Administered Glucose in Patients with Chronic Schizophrenic and Manic-Depressive Psychoses

DOROTHY H. HENNEMAN, M.D., Boston
MARK D. ALTSCHULE, M.D.,
and
ROSE-MARIE GONCZ, Waverley, Mass.

ABNORMAL changes in the concentrations of blood glucose and its breakdown products occur following the administration of glucose in patients with schizophrenic, manic-depressive, and involutional psychoses.[1] After the administration of glucose by mouth there is often a lag in the return to the fasting level of the blood glucose concentration and there is no fall below the fasting level at two or three hours. The patients often also show an excessive rise in the blood lactic and pyruvic acid concentration and a rise instead of the normal fall in the blood citric and α-ketoglutaric acid concentrations. In addition, many patients show an excessive and prolonged fall in serum inorganic phosphate level. All the patients studied here have shown at least three of these abnormalities, and some manifested all of them. The duration of mental illness appears to influence the incidence and degree of abnormality seen. Patients with psychoses of recent onset exhibit the abnormalities in the changes in the blood glucose, lactic acid, and pyruvic acid and in the serum inorganic phosphate concentrations more frequently and to a greater degree than do those patients with chronic psychosis. On the other hand, the abnormal rises in blood citric and α-ketoglutaric acid concentrations have been observed in all the patients with chronic psychoses studied (all of 13 receiving glucose by mouth) but in only two-thirds of the patients with psychoses of recent onset (7 of 11 receiving glucose by mouth).

Treatment that results in clinical remission in the patients with psychoses of recent onset is followed by reversal toward normal of the changes in the blood glucose, lactic acid, and pyruvic acid and in serum inorganic phosphate concentrations that occur after the ingestion of glucose. The type of clinical psychoses diagnosed cannot be correlated with the degree or type of abnormality observed. Patients with neuroses do not exhibit these abnormalities.

The study presented here was designed to clarify the observed differences between the patients with psychoses of recent onset and those with chronic psychoses. The metabolic effects of administered glucose were studied in patients with chronic psychoses before and again during the time that the subjects were under the influence of administered hydrocortisone or corticotropin (ACTH). This was done because available evidence [2] suggests that the adrenal cortex is hyperactive in patients with psychoses of recent onset but not in patients with chronic psychoses.

MATERIALS AND METHODS

Four patients, two men and two women, with chronic psychoses were studied. Their ages were 27 and 45 for the men and 29 and 42 for the women. One normal man, age 34, was also studied. All subjects were given a high-carbohydrate diet for three to five days before each test.

The methods used were the same as those already described.[1] All determinations of blood pyruvic acid concentration were made chromatographically.

Patients M, D, and H, and the normal subject, C, received 100 gm. of glucose by mouth before receiving hydrocortisone and again on the morning

From the Laboratory of Clinical Physiology, McLean Hospital, Waverley, and the Department of Medicine, Harvard Medical School, Boston; postdoctorate Fellow, U. S. Public Health Service, National Institute of Mental Health (Dr. Henneman).

after a three-day course of 50 mg. every 12 hours of hydrocortisone * (Figs. 1 to 4).

Patient E, a psychotic patient, received 50 gm. of dextrose by vein in 500 ml. of isotonic sodium chloride solution over a period of a half hour before receiving corticotropin and again on the morning after a three-day course of 20 mg. of corticotropin injected intramuscularly every six hours (Fig. 5).

OBSERVATIONS

Changes in Blood Glucose Concentration.—In three cases (M and E and the normal subject, Case C) the glucose tolerance was normal in the control period and was slightly impaired after the administration of hydrocortisone or corticotropin for three days. In two instances (Cases H and D) the glucose tolerance in the control period was impaired and appeared to be slightly improved when the administration of hydrocortisone preceded the administration of the glucose. However, the changes observed in all five subjects while under the influence of administered hormones were not outside the range of spontaneous variation.

Changes in Blood Lactic Acid Concentration.—In all four patients studied (Cases M, E, D, and H) and the one normal subject (Case C) the rise in blood lactic acid concentration following the administration of glucose alone was well within the normal limits described by others [3] and confirmed by us.[1] After a three-day course of administered corticotropin or hydrocortisone, all five subjects showed a rise in blood lactic acid concentration following the administration of glucose which was much greater and was well above the range normally expected after the administration of glucose alone.

Changes in Blood Pyruvic Acid Concentration.—All five subjects had normal changes in blood pyruvic acid concentration when glucose alone was given. After a three-day course of hydrocortisone (Case M) or of corticotropin (Case E) the rise in blood pyruvic acid concentration observed after the administration of glucose was markedly increased and was well above the normal range. In the remaining two patients (Cases H and D) and the normal subject (Case C) the prior administration of hydrocortisone had no effect on the changes in pyruvic acid concentration observed after the administration of glucose alone.

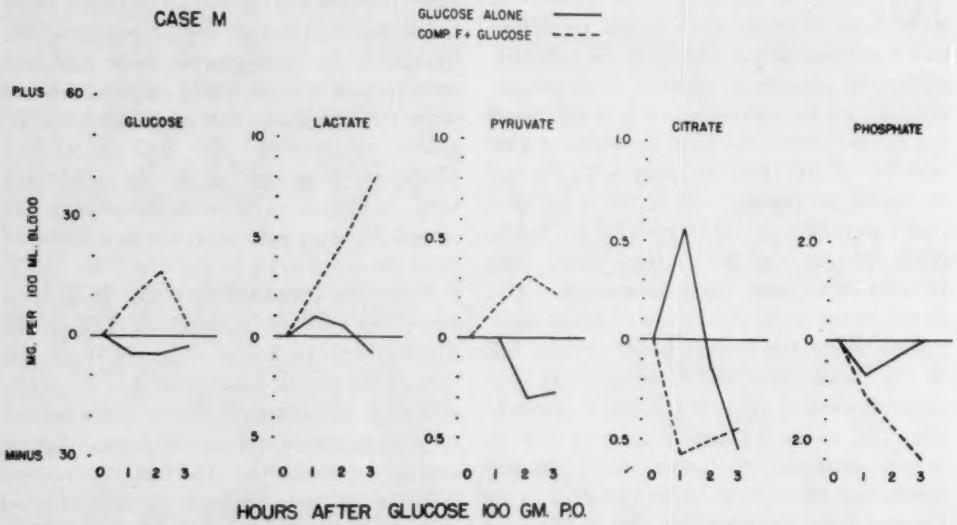


Fig. 1.—Effect of the oral administration of glucose in a chronic female manic patient before (solid line) and after (broken line) a three-day course of hydrocortisone.

Changes in Plasma Citric Acid Concentration.—In all four patients with chronic

* Supplied by Merck & Company, Inc., Rahway, N. J.

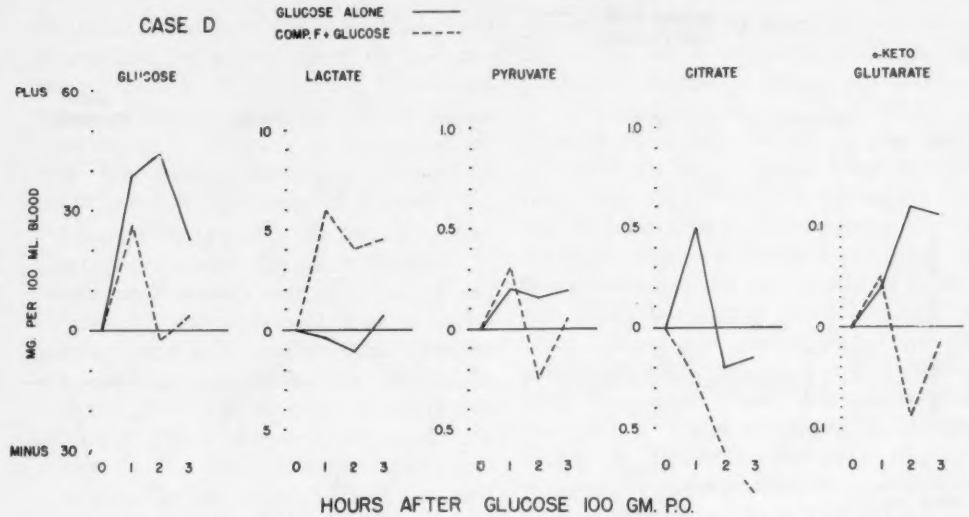


Fig. 2.—Effect of the oral administration of glucose in a chronic female schizophrenic patient before (solid line) and after (broken line) a three-day course of hydrocortisone.

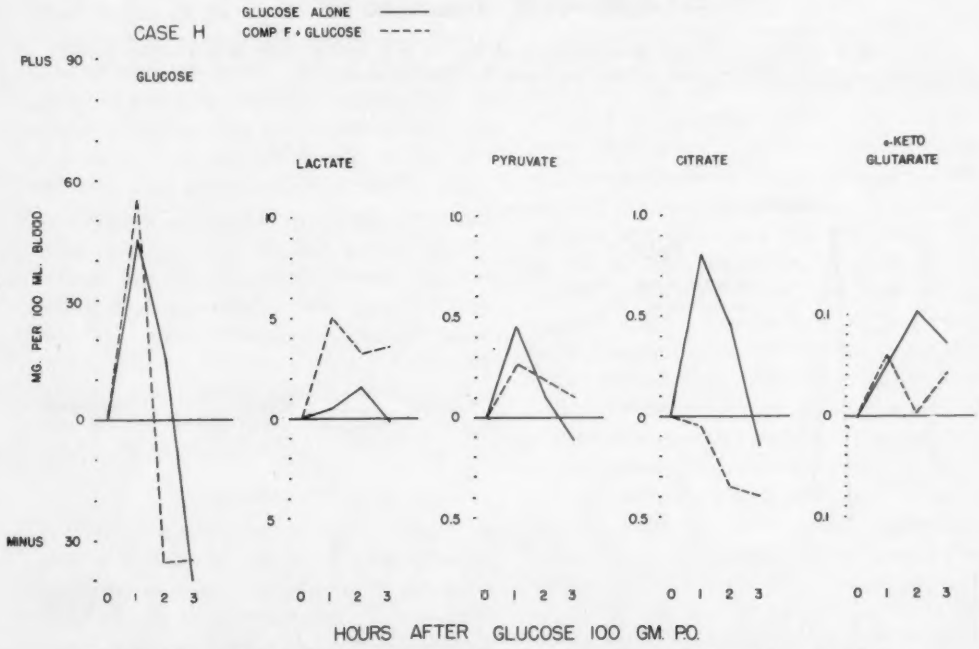


Fig. 3.—Effect of the oral administration of glucose in a chronic male manic patient before (solid line) and after (broken line) a three-day course of hydrocortisone.

psychoses (Cases M, E, H, and D) the administration of glucose in the control period was followed by a rise instead of the reported normal fall † or absence of change in plasma citric acid concentration; the normal subject (Case C) showed no significant change in blood citric acid concentration following the administration of glucose. When glucose was administered after a three-day course of either hydrocortisone or corticotropin the

† References 1 and 4.

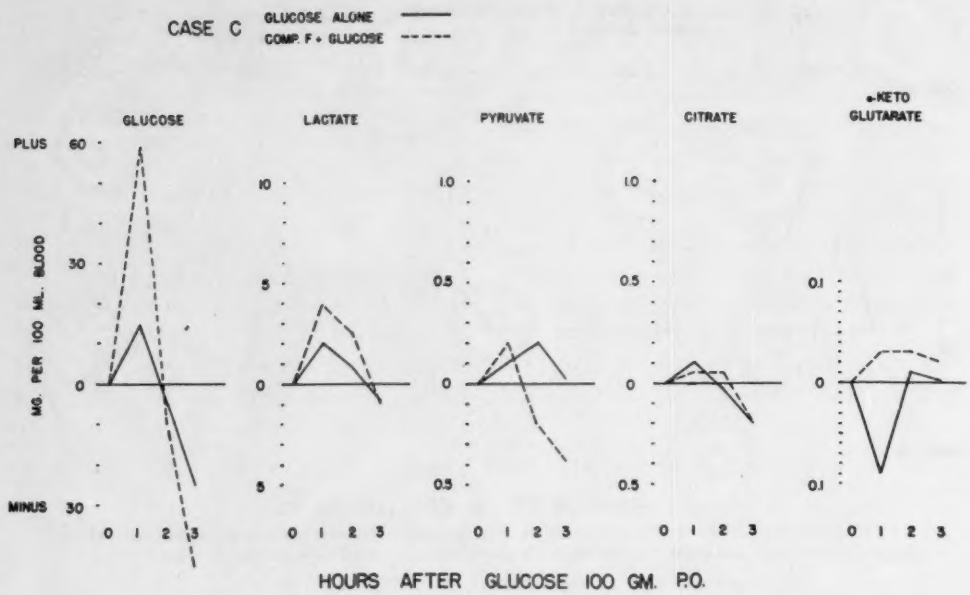


Fig. 4.—Effect of the oral administration of glucose in a normal male subject before (solid line) and after (broken line) a three-day course of hydrocortisone.

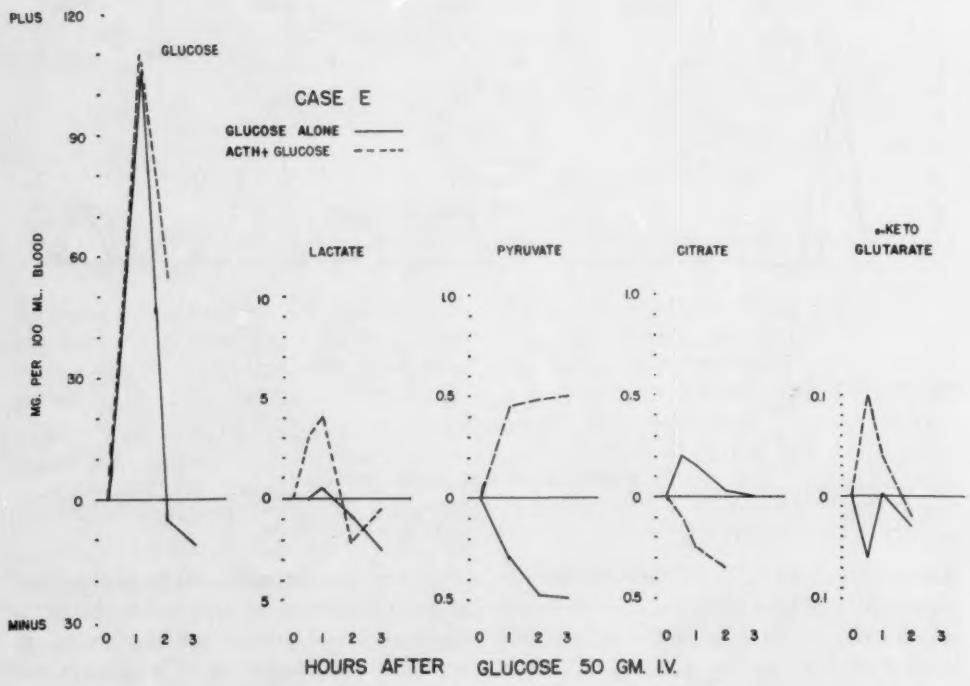


Fig. 5.—Effect of the intravenous administration of glucose in a chronic male schizophrenic patient before (solid line) and after (broken line) a three-day course of corticotropin.

abnormal rise in citric acid concentration was changed to the normal fall in the four patients (Cases M, E, H, and D). The normal subject (Case C) again showed no significant change in citric acid concentration, despite the administration of hydrocortisone prior to the administration of glucose.

Changes in Blood α-Ketoglutaric Acid Concentration.—In the three patients in whom measurements were made, two (Cases D and H) had abnormal rises in blood α-ketoglutaric acid concentrations after the administration of glucose alone. When glucose was given after the prior administration of hydrocortisone, one case (Case D) showed a normal fall in blood α-ketoglutaric acid concentration and the other (Case H) showed no significant difference from the control study. One patient (Case E) and the normal subject (Case C) had the normal fall in α-ketoglutaric acid concentration following the administration of glucose alone; when glucose was given to these subjects after the prior administration of hydrocortisone (Case C) or corticotropin (Case E), the α-ketoglutaric acid concentration showed a rise.

Changes in Serum Inorganic Phosphate Concentration.—In the one patient studied (Case M), the change in serum inorganic phosphate concentration was normal following the administration of glucose alone. When glucose was given after the prior administration of hydrocortisone for three days, the fall in serum inorganic phosphate was strikingly increased.

COMMENT

The administration of corticotropin or hydrocortisone for three days prior to the administration of glucose altered the metabolic effects of administered glucose strikingly in four patients with chronic psychoses but only slightly in one normal subject. Glucose tolerance was perhaps slightly decreased in three subjects (one of them the normal subject); lactic acid accumulation was increased in all five subjects; pyruvic acid accumulation was increased in two of the patients; the abnormal rise in plasma citric acid concentration observed after the administration of glucose alone was reversed to the normal fall in the patients with chronic psychoses, whereas no change was observed in the normal subject; the abnormal rise in α-ketoglutaric acid concentration observed in two patients with chronic psychoses after glucose alone was reversed to the normal fall, and the fall in serum inorganic phosphate was markedly increased in the one patient in whom measurements were made. It is difficult to say whether or not the changes in blood glucose and α-ketoglutaric acid are outside the range of spontaneous variation; their inconsistent occurrence suggests that they are not. The consistency of the changes induced by the administration of the hormones prior to the administration of glucose in concentrations of lactic and citric acids, however, indicates that these were not due to spontaneous variation.

The data strongly suggest that the administration of corticotropin or hydrocortisone prior to the administration of glucose changed the metabolic effects of administered glucose so that four patients with chronic psychoses exhibited changes remarkably similar to those previously described in patients with psychoses of recent onset.[1] The reason for this alteration in metabolic response is not understood, but the findings suggest that the previously described metabolic differences between patients with psychoses of recent origin and those with chronic psychoses may be due to adrenocortical hyperactivity in the former. This adrenocortical hyperactivity present in psychoses of recent onset is only temporary, and it is probably on the periphery of the fundamental metabolic error present in the mental diseases considered here. The changes induced by the administration of corticotropin or hydrocortisone prior to the administration of glucose suggest that these hormones inhibit the metabolic pathways whereby pyruvate and lactate enter the tricarboxylic acid cycle and potentiate the pathways whereby citrate is utilized.

SUMMARY AND CONCLUSIONS

The changes in the blood concentrations of glucose and of lactic, pyruvic, citric, and

α-ketoglutaric acids after administration of glucose were studied in four patients with chronic manic-depressive or schizophrenic psychoses; all four patients showed abnormal utilization of the glucose in a pattern previously shown to occur commonly in chronic psychoses. Administration of hydrocortisone (three cases) or corticotropin (ACTH) (one case) for three days prior to the administration of glucose altered this pattern of disordered glucose metabolism so that the changes observed resembled those more commonly found in patients with psychoses of recent onset.

The significance of these findings is discussed.

REFERENCES

1. Henneman, D. H.; Altschule, M. D., and Goncz, R. M.: Carbohydrate Metabolism in Brain Disease: II. Glucose Metabolism in Schizophrenic, Manic-Depressive, and Involutional Psychoses, A. M. A. Arch. Int. Med. **94**:402, 1954.

2. Altschule, M. D.: Bodily Physiology in Mental and Emotional Disorders, New York, Grune & Stratton, Inc., 1953, pp. 136-142.

3. Edward, H. T.: Human Respiratory Quotients in Relation to Alveolar Carbon Dioxide and Blood Lactic Acid After Ingestion of Glucose, Fructose, or Galactose, J. Nutrition **27**:241, 1944.

4. Natelson, S.; Pincus, J. B., and Lugovoy, J. K.: Response of Citric Acid Levels to Oral Administration of Glucose: I. Normal Adults and Children, J. Clin. Invest. **27**:446, 1948.

Treatment in Internal Medicine

MANAGEMENT OF CHRONIC NEPHRITIS

GUY W. DAUGHERTY, M.D., Rochester, Minn.

THE MANAGEMENT of chronic nephritis is one of the problems that is faced by all internists who do not sharply limit their field of interest. Even those who do ultimately become concerned with the problem of renal function. For example, there is the endocrinologist who must treat his patient after the development of the Kimmelstiel-Wilson syndrome; the hematologist whose patient, suffering from multiple myeloma, develops renal insufficiency, and the gastroenterologist whose patient, suffering from cirrhosis, develops associated hepatic and renal failure. Progress has been made in the management of chronic nephritis in recent years, but that progress has been made slowly and unspectacularly.

AIMS IN MANAGEMENT

By careful and continuous supervision the internist can accomplish much for the patient with chronic nephritis. Although cure, which would of necessity involve the replacement of damaged or destroyed functional units of the kidney, is impossible, the patient may be helped to lead a productive and comfortable life. He may be tided over the period of sudden worsening of his renal insufficiency caused by an acute infection. He may be saved from fatal potassium intoxication secondary to an injury or operation attended by disturbance in water balance. Finally, he may be made more comfortable by measures designed to control acidosis, nausea, dehydration, and other symptoms seen in the advanced stages of chronic nephritis.

From the Section of Medicine, Mayo Clinic and Mayo Foundation.

The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

In certain patients with chronic glomerulonephritis of fairly long duration and with severe renal insufficiency, the lesion seems to be at least partially reversible. In the absence of specific therapy, improved function would raise the question as to whether there may not be an occasional patient in whom restitution of functional units or "healing" may take place even though the process would appear by usual criteria to be chronic. Although there is no way of recognizing this group beforehand, their maintenance through a period of severe renal insufficiency is certainly most rewarding.

CAUSES OF CHRONIC RENAL INSUFFICIENCY

When the physician considers the problem of chronic nephritis he generally thinks of the later stages of the specific renal disease glomerulonephritis, which, at its inception at least, was associated with a type-specific hemolytic Streptococcus. Actually, the presenting clinical manifestations in the later stages of renal disease are somewhat similar, whether the original disorder was glomerulonephritis, pyelonephritis, or polycystic disease of the kidney. Similarly, in certain cases of hypertensive vasculorenal disease the picture is that of renal insufficiency indistinguishable clinically, and distinguished with great difficulty pathologically, from the later stages of glomerulonephritis.

In addition to the above-mentioned conditions, the later stages of somewhat more unusual renal disorders may present many problems in management that have features in common with the management of glomerulonephritis. In these conditions the renal lesion is usually one manifestation of a multisystem disease. These disorders include amyloid disease involving the kidney, lymphoblastoma of the kidney, lupus erythematosus, periarteritis nodosa, chronic vitamin D intoxication, overfunctioning of the para-

thyroids, the milk-alkali syndrome, sarcoidosis, and obstruction of the lower part of the urinary tract with back-pressure atrophy of renal substance. Although the nephrotic syndrome, with its picture of edema, albuminuria, hypoproteinemia, and hypercholesterolemia, is frequently seen as a stage in glomerulonephritis and more rarely in other chronic renal disorders, its management will not be discussed at this time.

NATURE OF ABNORMAL RENAL FUNCTION

Structural Bases of Abnormal Renal Function

Glomerular Lesions.—When a proliferative process such as glomerulonephritis affects the kidney and has progressed to the point that a large enough number of glomeruli are severely enough affected, there is a fall in the glomerular filtration rate and the actual load of solute filtered is reduced. Involvement of the glomerulus by a process such as intracapillary glomerulosclerosis or amyloid deposition likewise decreases glomerular filtration. Such a decrease in filtration is ultimately a factor in failure of the excretory function. The magnitude of the decrease in glomerular filtration may be quite large, ranging from the normal of 130 cc. per minute to the order of 10 to 40 cc. per minute. Occasionally, it would appear that the tubular reabsorptive function is not decreased to the degree that glomerular function is decreased. This circumstance, when coupled with decreased filtration, further interferes with the excretory and regulatory ability of the kidney.

Tubular Damage.—When the damage to the tubules is of sufficient magnitude, there are loss of secretory function of the renal tubular cells and loss of the tubule's normal ability to conserve base by the manufacture and substitution of ammonium ions for cations of the filtrate, the reabsorption of all filtered bicarbonate, and the substitution of hydrogen ions for cations in the filtrate. Under these circumstances a serious acid-base disturbance, namely, acidosis, tends to develop and electrolyte depletion becomes a matter of concern. Apparently in some conditions, for example in certain cases of pyelonephritis, tubular function is more depressed than glomerular function.

Vascular Changes.—Advanced atheromatous changes affecting a renal artery or its branches may result in nonfunction and gross loss of parenchyma, with scarring in the regions supplied by the affected artery. These lesions usually occur in the aged and often are not clinically significant. On the other hand, the advanced sclerotic changes of the renal arterioles associated with arterial hypertension generally result in a significant reduction in the total renal blood flow and later a decrease in glomerular filtration. In advanced nephritis, however, both glomerular and tubular function are severely reduced.

Consequences of Abnormal Renal Function

Electrolyte Disturbances.—Retention of specific radicals and substances such as phosphate, sulfate, urate, urea, and creatinine usually occurs. Calcium and, rarely, sodium tend to be lost in excess of intake; the latter more frequently is retained in excess of losses. Ions, such as potassium and chloride, may be abnormally retained or lost, potassium retention often constituting a serious problem in management in the later stages when the volume of urine is small.

Disturbance in Water Balance.—In advanced renal insufficiency water balance is frequently abnormal. Most often this abnormality takes the form of edema. At times it seems to be due to the kidney's inability to handle water in its usual manner, perhaps as a result of hormonal influences or as yet poorly understood volume-regulating mechanisms. In these instances the sodium space is expanded by increased total body water and possibly an intracellular movement of sodium. Often the concentration of sodium in the serum is below normal values.

In certain instances dehydration may be the abnormality in water balance. Most frequently this is seen in instances of reduced fluid intake attributable to nausea or fluid loss due to vomiting. In the latter instances

there may be an associated serious electrolyte disturbance due to losses in the vomitus.

Disturbances in Water and Electrolytes.—Combined water and electrolyte disturbances are commoner than either water disturbances or electrolyte disturbances alone. The most frequent of these is that seen in the edema of congestive heart failure. Here the total body sodium is increased in proportion to water retention so that the concentration of serum sodium remains relatively normal.

The nephrotic type of edema with its marked hypoalbuminemia is not commonly seen in chronic glomerulonephritis with advanced renal insufficiency. When it does occur, it may pose a major difficulty in diet, water, and electrolyte therapy.

MEASUREMENT OF FUNCTIONAL ABNORMALITY

Investigative Procedures. — There are quite accurate methods which will indicate the several functions of the kidney. Inulin or mannitol clearance will be at the rate of glomerular filtration; iodopyracet (Diodrast) and *p*-aminohippurate clearances at a low concentration in the plasma indicate the effective renal plasma flow, while clearance of iodopyracet and *p*-aminohippurate when the plasma concentration is high measures tubular excretory ability for the particular test substance. Likewise, the tubular reabsorptive function for glucose can be calculated. While these methods are of value and may be carried out in investigative studies, they are not available for the management of patients generally. Hence, other means of estimating the factors in functional ability must be used.

Common Clinical Tests.—Blood Urea Clearance Tests: On the whole, tests in general use, properly interpreted, give a reasonably accurate indication of function. The most commonly employed means of estimating glomerular filtration are determination of the blood urea or nonprotein nitrogen and determination of the urea clearance. Provided the volume of urine is adequate so that osmotic factors influencing the back diffusion of urea from the distal tubular filtrate do not distort the results and provided there is no obstruction of the lower part of the urinary tract to interfere with accurate collection of the timed specimen of urine, the urea clearance value reflects glomerular filtration rate. The level of urea in the blood varies inversely with the urea clearance, although the relationship is an approximate one. High values for blood urea when the properly obtained values for urea clearance are not proportionally depressed may be attributable to excessive production of urea, as from elevation of body temperature or excessive ingestion of protein. Similar relationships may obtain in instances of dehydration from any cause. The creatinine content of plasma, like the urea content, may be used as an indicator of glomerular filtration rate. Unlike the urea content, the creatinine content of plasma is less affected by such factors as excess protein catabolism and dehydration and is therefore a preferable indicator. Reduction in the glomerular filtration rate is frequently seen in those diseases, mentioned previously, in which the glomerulus is primarily affected and in the later stages of those diseases in which the arterial supply to the kidney is compromised.

Concentration Tests: The urine-concentration tests of Mosenthal or Addis, or modifications thereof, in which the specific gravity of the urine is determined after a period of dehydration to insure near-maximum concentration, give an indication of the concentrating ability of the distal convoluted tubules. The tubular cell must reabsorb water against an ever-increasing osmotic gradient caused by the solute in the tubular fluid. Certain central nervous system factors at times influence this renal mechanism and make proper interpretation of the test important. Impaired ability to concentrate the urine occurs early in disorders affecting the lower nephron, such as pyelonephritis. As previously indicated, in many renal diseases the lesion is diffuse, affecting the glomeruli, tubules, and vessels, with consequent loss, relatively early in the disease, of ability to concentrate the urine.

Dye-Excretion Tests: Additional evidence of the functional state of the renal tubules may be had by determining the kidneys' capacity for excreting phenolsulfonphthalein. The result of this determination is affected by the excretory capacity of the tubules and the effective renal blood flow. Most of the dose of injected dye is removed by tubular excretion. Quantitative alterations in the rate of excretion of phenolsulfonphthalein in the diseased kidney are in the same direction as alterations in iodopyracet and *p*-aminohippurate clearance. The rate of phenolsulfonphthalein excretion may be compared then to known normal values. This simple clinical test gives helpful information; it is technically different from, and much simpler than, a phenolsulfonphthalein (phenol red) clearance study. In advanced states of impaired renal function the development of acidosis or the wastage of sodium in the face of low values for serum sodium is indicative of serious derangement of distal tubular function.

DETERMINING CAUSE OF RENAL LESION

History.—Information not directly concerned with the functional aspect of a renal disorder is important in determining the cause of the lesion. Characteristic historical data may play a large part in indicating the answer to this question, whether the disease be chronic glomerulonephritis or some other type of chronic renal insufficiency mentioned above. The nature of its onset and its course and particularly the presence of symptoms or findings of involvement of other organs may be extremely important in elucidating the disease responsible for the chronic renal insufficiency.

Physical Examination.—The items in the physical examination that are important in determining the cause of the renal lesion are the size of the renal mass as determined by palpation, the presence or absence of edema, and the presence of hypertension. In certain diseases in which the renal involvement is part of a process involving other organs, the physical manifestations of the disease in some other organ may indicate the diagnosis. Examples of this are the skin lesions of lupus erythematosus or the nodal involvement of lymphoma. Pallor of the mucous membranes, indicating anemia, and a uriniferous odor of the breath may be noted in advanced renal insufficiency but are of little value in differentiating the causes of renal insufficiency.

Laboratory Tests Other Than "Function" Tests.—Urinalysis, with culture of the urine if infection is suspected, often yields valuable information. Excretory urography may be carried out if renal functional impairment is not great enough to interfere with the concentration and excretion of the radiopaque material. If the renal insufficiency is so great that the kidney cannot excrete the radiopaque material, a roentgenogram of the kidneys, ureters, and bladder may yield helpful information as to the size of the renal mass, renal lithiasis, or congenital defects, including polycystic disease. In certain instances cystoscopy with retrograde pyelography is indicated. Further help in defining the nature of the renal lesion may be had from determination of the values for blood hemoglobin and serum protein and, rarely, from such tests as the Congo red test for amyloid, bone-marrow biopsy for myeloma, or the L. E. clot test for acute disseminated lupus erythematosus.

As indicated previously, management of the various types of chronic renal disease, exclusive of the nephrotic syndrome, when they have reached the stage of renal insufficiency, is in general quite similar. The importance of defining the nature of the renal lesion lies mainly in attempting a prognosis. While there is great variability in all groups, one may see, for obvious reasons, his efforts rewarded by little success in managing the renal insufficiency of malignant vasculorenal disease or diabetes (Kimmelstiel-Wilson syndrome), while the patient having polycystic disease or chronic pyelonephritis may do well for a surprisingly long time.

SYMPTOMS OF CHRONIC NEPHRITIS

Occasionally persons with chronic nephritis attended by a mild degree of renal insufficiency, as indicated by the various tests men-

tioned above, feel quite well, carry on a normal program of activity, and indeed may be completely unaware that they are afflicted with any disease. The symptoms of chronic nephritis are interesting in that, when they develop, they are generally not those of the nephritis directly but some bodily derangement, more or less correctable, secondary to functional failure of the kidney.

General Systemic Manifestations.—Weakness or exertional dyspnea related to anemia may be the symptom that causes the patient to seek advice from his physician. Sometimes the initial and presenting symptom is anorexia or nausea. It is not at all unusual for a patient to recount the story of polyuria, increased fluid intake, and what he terms a "bad taste" in the mouth. Although occurring only when there is severe renal insufficiency, hiccough may be a very troublesome symptom.

Symptoms Related to Hypertension.—Another group of symptoms consists of those related to arterial hypertension. Headache is one of the commoner of these. It is at times severe and occasionally intractable. Another symptom related to hypertension, and the associated vascular disease, is sudden and severe reduction in visual acuity. Occasionally this visual loss provides the impetus which leads the patient to seek medical attention. Somewhat rarer is the sudden onset of diplopia due to the fact that a tiny vascular lesion of the brain stem has involved a nucleus of the cranial nerves that control eye movements. Finally, the entire symptom complex of congestive heart failure may be present in those patients who have had hypertension long enough and severely enough to cause myocardial insufficiency. In addition to the edema of congestive heart failure, evidence of fluid retention may more rarely be present, as previously mentioned, on a nephrotic basis or the basis of poorly understood hormonal or electrolyte disturbances in the terminal phase of chronic nephritis.

Symptoms Related to Abnormal Fluid and Electrolyte Concentrations.—Symptoms of advanced renal insufficiency include hyperpnea, which may be extremely distressing in the patient who has severe, uncompensated acidosis. The differentiation of this symptom from the dyspnea of congestive heart failure is important from a therapeutic standpoint. Tetany, in our experience at the Mayo Clinic, has been extremely rare, although it has been seen in young adult patients. This symptom, which is related to calcium disturbance, is to be distinguished from muscular twitchings seen in the terminal stages of uremia. The exact cause of muscular twitchings, a phenomenon of increased irritability, has not been satisfactorily defined. It is probable that both the twitchings and the convulsions of terminal uremia likewise may be the result of several separate factors. They constitute the most dramatic and, to the patient's relatives and often to the patient, the most distressing of all the symptoms of chronic nephritis. Extreme weakness and even paralysis due to hypokaliemia have been reported. A hemorrhagic tendency, seen in some patients, may be expressed in severe bleeding or chronic oozing from the mucous membranes.

MANAGEMENT OF CHRONIC NEPHRITIS

Prevention.—It is in order in a discussion of chronic nephritis to speak of measures which will possibly prevent the development or progression of this disorder. The actual mechanism by which acute glomerulonephritis develops is still not understood. It is thought that infection by a Group A Streptococcus is usually responsible for initiating the process, but certainly in many instances such an infection, if it occurs, goes unnoticed. The great variability of the incidence of acute glomerulonephritis and its apparent lack of relation to acute rheumatic fever, another disease thought to follow streptococcal infection, has long been a puzzling fact. Work by Rammelkamp and others has suggested that, of the Group A hemolytic streptococci, certain strains tend to be nephritogenic. He found that in a large percentage of cases of acute glomerulonephritis there was an associated infection by Type 12, Group A hemo-

lytic streptococci. It has been suggested that the periodic appearance of Type 12 streptococci would explain the variable incidence of the disease. If this is true it would suggest that the incidence of glomerulonephritis might be reduced by the prophylactic treatment of the family and close associates of the patient with acute glomerulonephritis. Indeed, such an accomplishment is suggested, although not conclusively proved, by Kleinman's experience with mass prophylactic treatment with penicillin in an epidemic of acute glomerulonephritis on the Red Lake (Minnesota) Indian Reservation. While an acute infection of the nose and throat in a patient with acute glomerulonephritis should certainly be treated, it is somewhat doubtful that treatment of this particular established infection will be early enough to alter significantly its effect on the kidney. Because the incidence of acute glomerulonephritis is so low, and that of upper respiratory infections so high, it will be very difficult to determine whether treatment of respiratory infections generally reduces the incidence of renal disease, but hope that it may is not unfounded. Patients with chronic glomerulonephritis who are prone to have repeated respiratory infections should be given penicillin continuously as a prophylactic measure against such infections.

An infection which acts more directly than others upon the kidney to produce damage is the one that causes chronic pyelonephritis. Here any one of many organisms may be responsible for the infection, and a wider range of therapeutic agents may have to be employed. Certain primarily urologic conditions which, by interference with normal drainage, contribute to continued difficulty in eradication of an infection should be treated as indicated. Recurrence of infection demands, of course, reinstitution of treatment. Many times in chronic pyelonephritis the active infection has long since disappeared and the problem remaining is simply that of the renal insufficiency due to the damage caused by the previous infection. In such instances a history of previous infection may be the only indication of the nature of the primary disorder. Such a history points up the urgency of prompt and vigorous treatment of this type of infection when encountered prior to the stage of chronic renal insufficiency.

Diet.—For the patient with "latent" chronic nephritis of any type, but without renal insufficiency or edema, my colleagues and I usually advise no special dietary program other than one that supplies in adequate amounts the several requirements of the body. Such a diet usually contains 60 to 70 gm. of protein. In the presence of renal insufficiency as evidenced by increased concentration of blood urea we restrict the intake of dietary protein. Initially the intake is restricted to 30 to 40 gm. a day. An adequate caloric intake, mainly of carbohydrate foods, is urged. In selected patients we have encouraged the observance of "protein-free" days on which the patient reduces the protein intake as much as possible by eliminating completely the high-protein foods such as meat, eggs, milk, and cheese and by taking adequate quantities of those foods containing mainly carbohydrate and fat. The frequency with which this type of daily intake is employed depends on the patient's response to and acceptance of such a program. When used several days of each week it significantly decreases total protein intake. It is definitely a compromise with the extremely low-protein intake of diets such as the rice diet. The concentration of blood urea is distinctly lower on such a program, and it is our clinical impression that patients do better.

In the stages of severe renal insufficiency in which, because of various symptoms such as anorexia and nausea, the usual dietary intake is not well tolerated, an adequate intake of fat and carbohydrate must be provided for to avoid the metabolism of bodily protein that occurs in starvation. Commercial fat-carbohydrate emulsions are available and may be fed or administered by nasal tube. If the patient can retain nothing by mouth, dextrose solutions may be given intravenously to provide at least part of the desirable carbohydrate intake.

In many patients suffering from early to moderate renal insufficiency, fluid intake and polyuria are increased. This large intake is encouraged, and the patient is urged to take 2,400 to 3,000 cc. of fluid per 24 hours. If nausea temporarily interferes with adequate intake of fluid, 5 or 10% solution of dextrose administered intravenously may be used as a supplement. In general, however, intravenously administered fluid has no therapeutic advantage over orally administered fluid, provided the latter is well tolerated. The uremic patient who has been vomiting may actually be dehydrated. Although this can occur in the presence of edema, it more often is seen in its absence and may be associated with considerable depletion of sodium and chloride. In these instances water alone, that is, dextrose solutions, will not repair the deficit; chloride and sodium must be administered in addition to water.

Electrolyte Balance.—Because of variations in the lesions of those portions of the nephron that regulate the electrolyte composition of the blood, a number of disturbances in the electrolyte structure may be encountered. Initial and often-repeated determinations of the concentration of the various electrolytes are a prerequisite for intelligent therapy. In the absence of edema and the presence of a normal electrolyte pattern there is probably no valid reason to restrict the intake of salt.

Metabolic Acidosis: The usual disturbance seen in renal insufficiency is a metabolic acidosis owing to loss of the tubules' base-conserving function mentioned previously. When the degree of acidosis has become severe enough that compensating mechanisms are unable to meet the demands put on them, symptoms develop and treatment becomes necessary for the comfort of the patient. Hyperpnea due to acidosis may be rather readily controlled by the administration of sodium lactate or sodium bicarbonate. These may be given orally if tolerated or parenterally if necessary. Usually 75 to 100 mEq. of sodium is adequate initially. The level of plasma carbon dioxide is not always a reliable indication of the degree of compensation of an acidosis in renal insufficiency as compared with that in some other conditions, such as diabetic acidosis. Renal retention of certain anions such as phosphate and sulfate results in depression of plasma carbon dioxide, and hyperpnea from acidosis is likely to develop at a higher level of plasma carbon dioxide in a condition such as diabetic acidosis. The administration of sodium to the patient with acidosis and edema often causes further retention of fluid, but this can be accepted if distressing hyperpnea can be relieved.

Salt-Losing Syndrome: A very unusual electrolyte disturbance in patients with renal disease is that of sodium, and usually water, depletion caused by "losing" or "wasting" of sodium by the kidneys. This "wastage" apparently occurs apart from the loss resulting from failure of the kidneys' acid-base regulating mechanisms. Dietary restriction of sodium of course magnifies the defect. The condition is recognized on the basis of low values for serum sodium and persistent urinary loss of sodium despite exclusion of acidosis and adrenal insufficiency as possible causes for sodium loss. Once recognized, the condition is managed by sodium administration commensurate with sodium losses.

Potassium-Losing Syndrome: Also very rare is the patient who because of renal damage exhibits an inability to retain potassium. Here again, as with sodium wasters, the loss is over and above that which results from acidosis. Hypokaliemia may result, as previously mentioned. The treatment is potassium replacement. Orally administered potassium salts are quite satisfactory.

Potassium Retention: A much more frequent finding, as regards potassium, is potassium retention that occurs late in renal insufficiency, most often when the volume of urine is small. This electrolyte disturbance may be evidenced clinically by characteristic effects on the electrocardiogram, namely the appearance of high peaked T-waves, prolonged QRS-interval, and loss of P-waves. Its management consists of restriction of foods high in potassium content and the oral or rectal administration of a cation exchange resin in the hydrogen or ammonium cycle. In the use of a resin caution is necessary to

avoid further disturbance of the acid-base balance.

Hyponatremic State: Another electrolyte disturbance not infrequently observed is that in which the value for serum sodium is significantly below normal but in which there has been no marked loss of body sodium. Values for plasma chloride are generally also lower than normal. This condition occurs preterminally in some cases of glomerulonephritis and is also seen in many other conditions in which the patient is extremely ill, both in the presence and in the absence of detectable edema. Efforts to raise the sodium levels toward normal in these patients are almost universally unsuccessful, regardless of route of administration or concentration of the administered salt. In the edematous patient the edema tends to increase, and in the nonedematous, edema may appear.

Hypochloremic State: For reasons not entirely clear, plasma chloride values may be found depressed at times in the absence of or out of proportion to depression in serum sodium values. In these instances chloride can be administered in the form of ammonium chloride orally or intravenously, but such administration is usually not desirable because of the fact that the usual tendency to acidosis is increased.

Acid-Radical Retention: As previously indicated, phosphate and sulfate are retained in advanced chronic nephritis. Phosphate retention is usually associated with lowered serum calcium values. Disturbances of calcium metabolism, especially large renal losses, sometimes occur. The administration of aluminum hydroxide gels can be helpful in removing phosphate from the body by way of the gastrointestinal tract.

Treatment of Anemia.—Anemia is a common accompaniment of chronic nephritis. It is thought to be secondary to the effects of the retained waste products, but the question of whether it is due to depression of the hemopoietic function or increased hemolysis or both has not been entirely settled. At any rate iron, liver, and vitamin B_{12} are of essentially no value in correcting the anemia. Cobalt is apparently of some value in this type of anemia, but it tends to be poorly tolerated by the gastrointestinal tract. The severer degrees of anemia should be controlled by blood transfusion. Repeated small amounts of blood (250 to 300 cc.) given slowly are desirable, because of a somewhat greater tendency for such patients to have reactions.

Treatment of Hypertension and Congestive Heart Failure.—Patients suffering from chronic nephritis nearly always have hypertension. In some instances the hypertension is a major factor in the clinical picture, and congestive heart failure secondary to the hypertension may be dominant terminally. In a majority of cases it appears that the hypertension is necessary to maintain glomerular filtration at a satisfactory level, since reduction of blood pressure is associated with worsening of renal insufficiency, as measured by increasing levels of blood urea and creatinine. There are, however, certain patients, particularly those with a mild degree of renal insufficiency, who seem to do well when adequately treated with antihypertensive drugs now available. Then there is also the group with mild renal insufficiency and congestive heart failure secondary to hypertension, who represent the most favorable of these patients for treatment of hypertension. Careful observation of the patient's renal function is essential during the period of treatment.

In addition to the use of drugs to lower blood pressure, the treatment of congestive heart failure includes the administration of digitalis, the restriction of salt in the diet, and a program of decreased physical activity, just as for congestive heart failure in any other circumstance.

Management of "Uremic" Symptoms.—The term "uremia" is here used to indicate a state or symptom complex which is more than just an elevation of the values for blood urea and creatinine. Symptoms encountered are fatigue, weakness, vomiting, headaches, hiccough, pruritus, muscular twitchings, convulsions, and, finally, coma. Fatigue and

weakness may be lessened by the transfusion of blood. Nausea and vomiting often are persistent. In certain instances these symptoms are lessened by dimenhydrinate (Dramamine) or parachloramine hydrochloride (Bonamine). More recently chlorpromazine (Thorazine) has seemed quite effective. For severe persistent headache elevation of the head of the bed some 10 or 12 in. (25 or 30 cm.) is sometimes helpful. Another measure that is useful at times is lowering of elevated blood pressure by use of one of the drugs employed in the treatment of hypertension. Lumbar puncture with removal of 20 to 40 cc. of cerebrospinal fluid may dramatically relieve headache. It has also controlled convulsions in some instances. Pruritus responds poorly but may be treated with soothing lotions. Muscular twitchings and apprehension should be treated with sedatives. Terminal convulsions may require intravenous administration of a barbiturate for control.

GENERAL CONSIDERATIONS

The patient who has chronic nephritis with renal insufficiency is more dependent on his physician than is the patient suffering from any of many other chronic diseases. This is due to two things. One is the multiple functions that may be deranged, namely, excretory, water-regulating, acid-base-regulating, and possibly blood-pressure-regulating functions. The second is that with loss of the natural ability to regulate, as for instance acid-base balance, then certain measures need to be applied which will make the regulatory task easier or enhance the damaged organ's ability to perform the work. Each patient presents an individual problem and needs to be impressed with the necessity of remaining under the physician's close observation. The condition may change so that what is excellent advice at one period may be quite inappropriate at another time.

The physician, on his part, has a big responsibility as regards the patient's morale. To many, a diagnosis of nephritis, because of popular conception, is the source of deep anxiety. A somewhat optimistic attitude would certainly seem justified by the increase in practical knowledge of renal function and the problems of electrolyte and water management. The patient will certainly sense the increased confidence the physician feels in directing treatment as he has available accurate data from his colleagues in the laboratory. Admittedly, a point in renal failure incompatible with life continues to exist, but if that point is set back and the course approaching that point is made smoother then the effort expended by physician and patient has been rewarded.

Progress in Internal Medicine

SYPHILIS

Review of the Recent Literature

HERMAN BEERMAN, M.D.
IRA L. SCHAMBERG, M.D.
LESLIE NICHOLAS, M.D., Philadelphia
and
LAWRENCE KATZENSTEIN, M.D., Wilmington, Del.
With the Collaboration of T. Guthe, M.D., and C. J. Hackett, M.D., Geneva, Switzerland

THIS, THE nineteenth annual review of syphilis, contains contributions published during the period July 1, 1953, to July 1, 1954. The over-all trends in this material are along the lines discussed in the previous review.[1] In fact, presentations of the problems seemed to have become so repetitious and so suggestive that further work on a dead subject [2] was a waste of time for all concerned, and such a waste of space in important medical journals, that we were considering saying "amen" to these summaries. However, certain experiences we have had in which trainees in dermatology and syphilology have not only failed to recognize active syphilis but have also actually failed to consider this disease in the differential diagnosis have convinced us that, like typhoid fever, syphilis must always be kept in mind. Furthermore, several editorial accounts in medical and lay journals of the potential and actual resurgence of syphilis are indications of how critical is the present need for wider dissemination of knowledge about syphilis. For example, Sontheimer, in the *Ladies' Home Journal*,[3] speaks of "The Dread Comeback." *Time* magazine,[4] reporting the proceedings of the 1953 meeting of the American Academy of Dermatology and Syphilology, stated that

> It looked as though syphilis no longer required the services of specialists, or even much attention. Some hospitals reported difficulty in getting enough cases for long-term research. Before the week was well along, the specialists changed their minds. Syphilis, they heard, had gone down for a count of nine but is now up and swinging again.

The Journal of the American Medical Association, under the editorial caption, "Venereal Disease Control Is Not Automatic," [5] points out that although there has been a downward trend in reported cases of primary and secondary syphilis this may mean either fewer cases or a failure to find the new cases. Every year the number of reported cases of early latent syphilis has exceeded that of primary or secondary syphilis. This indicates that more than half of the cases of syphilis go into the latent phase undiscovered. It states further that, although great strides have been made in venereal disease control, complete control is far from being accomplished.

Another facet in this problem is afforded by the study by Lentz and Beerman.[6] In 1952 a questionnaire was mailed to 4,236 physicians practicing in Philadelphia. The physicians were requested to indicate whether they treated in private practice in 1951 syphilis in adult men, syphilis in adult women, syphilis in infants and children, gonorrhea in men, gonorrhea in women, and gonorrhea in preadolescents. Of the 4,236 physicians, 74.6% responded. An analysis of the responses showed that 3,112 patients had been treated for syphilis and that 5,869 had been treated for gonorrhea. Had all patients treated been reported, there would have been an increase of 59.9% in syphilis and an increase

From the University of Pennsylvania Departments of Dermatology, School of Medicine (Donald M. Pillsbury, M.D., Professor); Graduate School of Medicine (Herman Beerman, M.D., Chairman), and the Venereal Disease Control Section, Division of Preventive Medicine, Philadelphia Department of Public Health (Ira L. Schamberg, M.D., Chief). Dr. Guthe and Dr. Hackett are with the World Health Organization.

of 70.1% in gonorrhea incidence in the records of the Health Department. About 7% of the physicians had treated over 70% of the patients. Moore[7] notes in an editorial that fresh infections of syphilis reached a near epidemic peak in 1947 and then began a drop. The decrease in incidence by 1952 amounted to nearly 90% of the peak incidence. Despite this decline, the internist may encounter diagnostic and therapeutic problems of late syphilis for a generation to come. The peak of discovery of congenital syphilis was in 1941, with a progressive fall to 1952. Likewise, the *British Journal of Venereal Diseases*[8] states that, although there was about 8% increase in both male and female cases of gonorrhea in the second quarter of 1953 as compared with the first quarter of that year, the downward trend of early syphilis continues uninterrupted, albeit at slackening tempo, and the number of cases of late syphilis remains essentially unchanged. Factors such as the untraced contacts of late syphilis and the defaulting early syphilitics, which constitute a hard core of patients with early syphilis, make it obvious that the venereologist still has much to do to control venereal disease and its effects. Reduction in clinic facilities and control efforts at this time would be of little direct economy and would actually indirectly cost the country (British Empire) dear. In spite of these data and warnings, the appropriating agencies for the control of venereal disease have established the "ostrich" policy of cutting nearly all support for further control. Deeply concerned with the future of nation-wide venereal disease control in the light of a 76% cut in Federal appropriations from 1953 to 1955, and further concerned by the reported rise in venereal disease rates in 17 states, three national organizations,[9] The American Venereal Disease Association, Association of State and Territorial Health Officers, and the American Social Hygiene Association, set forth a document which can only be appreciated by being read in its entirety. This was transmitted widely in pamphlet form throughout the country to influential public health and political figures in an attempt to prevent and forestall further decreases in interest in and appropriation of funds for venereal disease control. The authors emphasize that complete control of the diseases is not imminent, that there has been no lessening in the public health importance of the venereal diseases, that present allocation of public funds is inadequate to deal with the size and complexity of the problem, and that there is a continuing Federal responsibility for the control of the venereal diseases. It is emphasized that reported cases of early syphilis may not reflect true incidence. Each case of early latent syphilis diagnosed means failure in discovery of primary and secondary syphilis in previous years. It is estimated that there are, in this country at present, over 2,000,000 people who need treatment for syphilis and that in the past year, of approximately 91,000 civilians who acquired syphilis, only 10% were diagnosed and treated in the primary or secondary stage. Almost a quarter of a million cases of gonorrhea were reported to State Health Departments in 1952. It is estimated that the annual incidence is more than 1,000,000 cases. Epidemologic effort is basic to venereal disease case-finding activity. A reduction in venereal disease funds means a reduction in trained interviewers, which, in turn, creates a grave deterioration of case-finding activity. In view of these facts, the authors urge that the Federal Government resume its leadership in and responsibility for venereal disease control, maintain a $10,000,000 Federal budget for venereal disease control in the immediate present, recognize that despite the decreases in the apparent number of venereal disease cases in the nation we may not be finding more than a fraction of the cases that do exist, adhere to a long-term plan for reducing Federal support for venereal disease control selectively and gradually on the basis of local needs, and provide for a specific allocation for grants to States exclusive of Public Health Service venereal disease allotments, in order to assure adequate funds to each state for specific problem areas and unforeseen venereal disease emergencies. Tables listing syphilis and gon-

orrhea case rates from 1919 to 1953, mortality due to syphilis, and estimated annual costs of uncontrolled syphilis are appended. This well thought-out and valuable analysis of the current venereal-disease-control picture warrants the careful consideration of every public-health-minded citizen.

There are certain other developments which have arisen because of the belief that syphilis and the other venereal diseases are no longer a real medical problem. The most outstanding of these is the passing of another landmark in the American literature on these diseases, namely, the *American Journal of Syphilis, Gonorrhea, and Venereal Diseases.* This *Journal,* begun in 1917, has been a consistently good source of information on the venereal diseases, notably syphilis. In the past 18 years, under the editorship of Joseph Earle Moore, this periodical has attained still greater eminence in the field of medical journalism. Its successor, *The Journal of Chronic Diseases,* is scheduled to appear January, 1955, with Moore as editor. This journal will deal with syphilis and the other venereal diseases among many other chronic diseases. Further indications of the present thinking in regard to syphilis are suggested by the fact that this review contains no material on a number of subjects usually considered rather important, for example: prophylaxis of human syphilis, immunity, Jarisch-Herxheimer reaction, and fever therapy.

Serodiagnosis has come in for additional attention, with concentration on cardiolipin antigen and the problem of biological false reactions. The literature on the treponemal immobilization test is voluminous. Among other presentations, a review and a book on the subject have appeared. The reports on the agglutination and other procedures mentioned in the previous review have as yet not been fully evaluated, although much may be anticipated for the future. The world problem of the treponematoses has received a justifiable amount of space in a number of periodicals. One of the obvious deficiencies of this review period is the relatively little really experimental syphilis reported on. Considering the expense and the growing attitude against study of the venereal diseases, this is not surprising. A few of the more inspired workers in this field, like Turner, of Johns Hopkins University, and Eagle and his group, as well as Probey, of the United States Public Health Service, and Morton, of the University of Pennsylvania, among others, are still faithful to this field. General problems in the diagnosis and treatment of syphilis are adequately discussed. The number of reports of aneurysms ruptured into various parts of the body are reminiscent of the past and are indicative of the possibilities of the future development of much visceral syphilis. The collection of papers in the *British Journal of Venereal Diseases* on fatal syphilis is another example of the same. There is a growing realization, long denied, that penicillin and the other antibiotics are not as safe as believed. Fatalities and anaphylactoid reactions, as well as other untoward effects, are becoming increasingly numerous. In this connection, the summary by Kern and Wimberley must be read by all physicians who administer penicillin. Fortunately for the penicillin-sensitive person, efforts are being directed to the possibility of desensitization or the simultaneous use of cortisone and other agents. In spite of the pessimism expressed in the previous and this review as to future interest in venereal disease (syphilis) control, the material available for analysis in this review period somewhat belies the lack of interest. Perhaps the workers in far-flung fields have at last found time to write up their experiences.

Good sources of information on various phases of syphilis have appeared during this review period. Wortmann[10] has again reviewed syphilis. His report covers the same time period as our last publication. An editorial in the *British Journal of Venereal Diseases*[11] discusses the unknown in yaws. The Fourth Report of the WHO Expert Committee on Venereal Infections and Treponematoses,[12] which has recently been published as No. 63 in the World Health Organization Technical Report Series, is, in effect,

a summary record of present knowledge concerning the control of treponemal diseases. It is particularly important as a source of information on the conduct of mass campaigns against nonvenereal treponematoses: yaws, bejel, pinta, "njovera," and endemic syphilis. Considerable experience in carrying out such campaigns has been gained in recent years, when many governments have undertaken large-scale control programs with the aid of international organizations such as UNICEF and WHO. The Committee's report covers all the phases of mass treponematoses: control programs, drugs and therapy, and serodiagnosis and other laboratory aspects; in addition, it deals briefly with personnel training for venereal-disease-control work, the control of venereal disease among seafarers, and nontreponemal venereal infections. Guthe and Willcox's [13] monograph on the treponematoses is a reprint of a special number of the *Chronicle of the World Health Organization*, 1954. It contains full discussion of changing concepts in the epidemiology and control of the treponematoses, national and international activities in treponematosis control, treponematosis control as a means to an end, and a selective WHO bibliography on treponematosis control. Idsøe, Guthe, Christiansen, Krag, and Cutler [14] have reviewed the various experiences in many parts of the world which have resulted in the acceptance of penicillin as the drug of choice in the treatment of syphilis. The first part of the paper deals with the laboratory and clinical basis for penicillin therapy including the time-dosage relationship, the importance of choosing preparations which cause a treponemicidal blood-level of long duration, and the mode of administration. The current concepts and problems of immunity in syphilis are also summarized, and an outline is given of the various serological studies undertaken since Wassermann developed the test bearing his name and which have led finally to the establishment of cardiolipin, beef heart, and egg lecithin as international reference preparations and the development of the Treponema pallidum immobilization and the Treponema pallidum agglutination tests. In the second part of the paper the authors consider the principles of follow-up and control of patients, with particular reference to relapses and reinfections; the present status of penicillin therapy, including acceptable dose schedules in early, latent, late and congenital syphilis, is also reviewed. The problems of the treatment of incubating syphilis and contacts are discussed at some length. The problem of endemic syphilis is discussed briefly in an editorial in the *British Journal of Venereal Diseases*.[15] Charpy's book [16] on the treponemal immobilization test is composed of a series of papers presented at a symposium at Marseilles, October, 1952, on this subject. Garcia's presentation [17] summarizes the results of work on neurosyphilis carried out in the hospital at Rio de Janeiro. It covers the whole of this aspect of syphilis but concentrates on tabes dorsalis and paresis.

HISTORY OF SYPHILIS

Interest in the history of syphilis goes on unabated. This year, a special one for those interested in this field, marks the centennial of the birthday of Paul Ehrlich. Celebrations have been held in many places and a number of chemotherapeutists and other scientists have written their thoughts about this father of chemotherapy. Every physician should read Hans C. S. Aron's [18] tribute at the centennial of the birthday of Paul Ehrlich. The biography is carefully written and reviews all of Ehrlich's life, from his first important paper entitled Mastzellen, written at the age of 23, to the interment of his mortal remains in the Jewish Cemetery of Frankfurt, at the age of 61. His influence on the chemotherapeutic research which was performed in the 20 years following his death is most remarkable, since we all recall part of the statement of Sir Henry Dale in 1949, "But the central idea of experimental chemotherapy, and the initial impulse of its triumphant march forward, came from Paul Ehrlich." Harrison [19] too has contributed an intimate memoir of the exciting days of 1910 when the clinical trials of Ehrlich's arsphenamide (Salvarsan) were being carried out

in a few selected centers. Marti-Ibanez [20] contributed a discussion of the mind and the world of Paul Ehrlich 1854-1954, and Nobel Prize Winner Waksman [21] has described Paul Ehrlich as man and scientist.

Other studies on the history of syphilis include those by Friedman,[22] by Hoffmann,[23] and by Weiss and Goldman.[24] Friedman, a third-year medical student, has reviewed the history of syphilis from the standpoint of its origin, evolution, and therapy in former times. Erich Hoffmann, from his 60 years of experience, reviews the methods of treating syphilis from the mercury era to the present. Weiss and Goldman present a photograph of a ceramic vase approximately 2,000 years old, from the Nazca period of the ancient Andean culture, which shows an ulcer over the prepatellar bursa which might be a gumma. This suggests that syphilis may have been present in Peru as long as 2,000 years ago. We are unable to make even a tentative diagnosis from the reproduction.

TREPONEMA PALLIDUM AND OTHER TREPONEMES

Most of the recent work on spirochetes deals with the effect of various agents, especially antibiotics, on their viability, etc. These data will be presented in the section on experimental syphilis. In addition, several papers dealing with other aspects of the treponemes will be detailed here.

Biological Investigations on Treponemes.—Comparative studies on T. pallidum, T. pertenue, and T. cuniculi by Turner, Hollander, and Schaeffer [25] have shown that the organisms have many common characteristics. Studies using the TPI test show no substantial immunogenic difference between T. pallidum and T. pertenue. Twelve strains of syphilis, bejel, or yaws from various parts of the world were isolated. The syphilis strains produced large and indurated lesions in rabbits. Yaws followed the usual pattern of a long incubation period with development of lesions less indurated and less extensive than those of syphilis. The effect of the bejel strains was between the other two groups. In vivo tests on the syphilis and Syria bejel strains indicated that they were as susceptible to penicillin as the Nichols strain. Except for the Indonesia yaws strain, all were tested in vitro, and none appeared more resistant to penicillin than the Nichols strain.

Total Vitamin Requirements of the Reiter Treponeme.—Steinman and his group [26] found that biotin nicotinic acid and pantothenic acid were essential for growth and viability of the Reiter treponeme. Thiamin increased the rate and amount of growth, while choline and riboflavin were merely acceleratory; *p*-aminobenzoic acid and the pyridoxine group of vitamins were inert.

Lennhoff's Spirochetes in Tissue.—After a study of 2,500 histologic sections from 58 excisions from different diseases, made according to the procedure outlined by Lennhoff, Loeb [27] found little to substantiate Lennhoff's published statement that he was able to demonstrate spirochete-like forms in numerous diseases of unknown cause. Furthermore, spirocheticides yielded completely negative results except in the case of a cutaneous-tumor-like lymphatic leukemia.

EXPERIMENTAL SYPHILIS

Experimental studies have been somewhat more prominent this year than last. As mentioned above, most of the reports deal with the effects of the antibiotics on spirochetes.

Search for Treponemes in Mice with Experimental Syphilis. — Attempts were made by Hård [28] to demonstrate T. pallidum in white mice infected with syphilis, using the methods of Lennhoff and Stroesco. Only in two instances were treponemes detected. No treponemes were found in the tissues of mice by means of dark-field phase-contrast microscopy and fluorescence microscopy.

Morphologic and Histochemical Sequences in Syphilitic and in Tuberculous Orchitis in the Rabbit.—Scott and Dammin [29] present a detailed study of morphologic and histochemical sequences in syphilitic and in tuberculous orchitis in the rabbit. They found fundamental differences in the course of

these processes. A predominantly stromal reaction was seen in syphilitic orchitis, in which the tissue was intensively metachromatic, relatively acellular, and contained large numbers of treponemes. In tuberculous orchitis there was early stromal and parenchymatous involvement, a good deal of cellularity, and little metachromasia. Tubercle bacilli are concentrated in the cellular portions of the tissue reaction.

Attempt to Produce a Penicillin-Resistant Strain of T. Pallidum in Experimental Syphilis.—Probey [30] made an attempt to induce penicillin resistance in the Nichols strain of T. pallidum in experimental syphilis by a large single subcurative dose of crystalline penicillin G. The study was made to determine whether a large dose of penicillin administered as a prophylactic agent in the presence of undiagnosed syphilis would render T. pallidum resistant. Tissue transfers from the 61 syphilitic rabbits treated with penicillin demonstrated that the therapy cured 54 rabbits, 26 of 30 infected with the resistant strain and 28 of 31 infected with the normal strain. In each of three consecutive rabbit passages, the Nichols strain was not rendered penicillin-resistant.

Action of Penicillin on T. Pallidum in Vivo.—Following addition of subtreponemostatic levels of penicillin to cultures of the Nichols and Reiter strains of avirulent T. pallidum, Morton and Ford [31] noted elongation of the treponemes, a phenomenon similar to that seen in penicillin-sensitive bacteria. However, when treponemes from early lesions of syphilis in the human being following administration of 40,000 units of aqueous penicillin G were studied by dark-field examination, no such elongation was noted. The organisms disappeared from syphilitic lesions within a few hours without undergoing changes in morphology. The authors suggest that this phenomenon can best be explained by lysis of the organisms by penicillin. Staphylococci pneumococci, and certain streptococci, as well as Clostridium perfringens, have been shown by other workers to be lysed by penicillin.

Comparative Sensitivity of Treponemes of Syphilis, Yaws, and Bejel to Penicillin in Vitro.—Nell [32] studied the in vitro sensitivity of treponemes of syphilis, yaws, and bejel to penicillin. Virulent treponemes from lesions of rabbit orchitis were suspended in the medium of Nelson and Diesendruck; varying amounts of penicillin were added, and motility counts were made. After incubation for 18 hours at 35 C. almost all treponemes were immobilized by a concentration of 10 mγ of penicillin per milliliter, whereas 75% remained mobile when a concentration of only 1 mγ of penicillin per milliliter was used. Fifty percent of the organisms were immobilized by 2 mγ of penicillin. By intracutaneous injection of penicillin-treponeme mixtures containing varying percentage of mobile organisms, it was determined that the virulence of motile organisms after exposure to penicillin is virtually unaffected and that treponemes immobilized by the penicillin are no longer viable. Susceptibility of treponemes to a given concentration of penicillin was found not to be influenced appreciably by the size of the inoculum. Increase of temperature in the range from 25 to 35 C. markedly increased the immobilizing effect of penicillin. With penicillin concentrations between 0.1 and 50 γ per milliliter there was a period of approximately four hours before any effect on treponemal motility was noted. This period increased, however, as the penicillin concentration was decreased below 0.1 γ per milliliter. No significant difference was found in the in vitro susceptibility to penicillin of seven strains of T. pallidum, two strains of T. pertenue, and three strains of bejel treponemes.

Comparative Effect of Various Antibiotics in Experimental Syphilis.—Turner and Schaeffer [33] studied the treponemicidal activity of seven antibiotics, utilizing a short in vivo method of assay. Rabbits were inoculated intracutaneously in eight sites on the clipped back. After lesions developed, a treponeme count was made from one of them. Animals with counts below 200 treponemes in 100 oil-immersion fields were not used.

Following treatment with various antibiotics, treponeme counts were made daily for six or seven days, the count being made each time on a previously unused lesion. Treponemicidal activity of the antibiotics was measured by a decrease in the number of treponemes. All the antibiotics tested exhibited definite antitreponemal activity in large doses. However, this was of a markedly lower order of magnitude than that exhibited by penicillin. The antibiotics studied were listed in order of decreasing effectiveness as follows: (*a*) penicillin, (*b*) carbomycin (Magnamycin) and erythromycin, (*c*) chlortetracycline (Aureomycin) and oxytetracycline (Terramycin), (*d*) choromycetin and streptomycin. The authors suggest that carbomycin and erythromycin be evaluated in the treatment of human syphilis.

Susceptibilities of Kazan, Nichols, and Reiter Strains of Treponema- and Pleuropneumonia-like Organisms to the Antibiotic Erythromycin (Ilotycin).—A study of the susceptibility to erythromycin of the cultivable treponemes (Nichols, Kazan, and Reiter strains) and pleuropneumonia-like organisms isolated from the human genitourinary tract was made by Keller and Morton.[34] Results showed that the treponemes were very susceptible to the action of the antibiotic, while pleuropneumonia-like organisms were highly resistant. The similarity of erythromycin to penicillin in its antibacterial spectrum was furthered by these results.

Study of the Treponemal Immobilizing Antibody in Syphilis.—Chacko[35] studied experimentally the relationship of reagin and treponemal antibody in syphilitic human and rabbit serums, with the use of the TPI test and standard tests. The titers of the immobilizing antibody and the Wassermann antibody or reagin were followed in untreated experimental rabbit syphilis by parallel quantitative tests of serums collected at monthly intervals and were found to follow different courses, showing little correlation with each other. The occurrence of a phenomenon of in vivo sensitization of T. pallidum by its own immobilizing antibody in rabbit testes was confirmed. The significance of this phenomenon is that it would cause false-positive tests for syphilis with the TPI test.

Commerical Prophylactics in Experimental Syphilis.—Carpenter and Boak[36] purchased 14 different prophylactic outfits sold for the prevention of venereal diseases. With one exception, for which information could not be obtained, the formula for each agent contained mercury. These 14 agents were evaluated in experimental syphilis. Only nine preparations protected rabbits from experimental syphilis one-half hour after exposure, and six preparations, after four hours' exposure to the Nichols strain of T. pallidum. Four prophylactics were noneffective when applied one-half hour and four hours after exposure. Another agent, which failed to protect rabbits one-half hour after inoculation, was not tested four hours after exposure but was assumed to be ineffective at that time. Three prevented experimental syphilis in rabbits one-half hour after exposure but were ineffective when applied four hours later. Experience has been gained to show that the experimental procedure employed is a relatively dependable index to the spirocheticidal action of an antisyphilitic drug. The tests indicate that many of the preparations on the market are not effective in preventing experimental syphilis of rabbits. Therefore, it is assumed that they would likewise be ineffective in the prevention of human syphilis.

Penicillin by Oral Administration in the Prophylaxis and Abortive Treatment of Experimental Syphilis of Rabbits.—Kolmer[37] studied the effect of penicillin by oral administration in the prophylaxis and abortive treatment of experimental rabbit syphilis. He reports that 200,000 units per kilogram of either buffered penicillin tablets or benzathine penicillin, administered 1 to 48 hours after intratesticular inoculation, is the minimal curative oral dose. He makes the unwarranted assumption that this same minimal curative dose holds for human beings and suggests that approximately 14,000,000 or more units of penicillin would be required

for prophylactic or abortive treatment of a 70 kg. man. Alexander and Schoch (Prevention of Syphilis, *Arch. Dermat. & Syph.* **59**:1, 1949) have shown that 900,000 units of absorption-delaying penicillin is effective by injection in the prophylactic treatment of human beings. It therefore appears highly probable that significantly less than 14,000,000 units administered orally would be effective in prophylaxis of human syphilis, especially if given within 24 hours of infection.

PROGNOSIS

A preliminary report by Danbolt and his colleagues [38] on the fate of syphilitics who receive no specific treatment shows promise of a really significant reevaluation of the hotly contested Bruusgaard figures. The need for information on the prognosis of syphilis untreated in its primary and secondary stages has been filled by a complete restudy of patients who were allowed deliberately by Boeck to remain untreated during the period 1891-1910. A representative 20% sample of these patients was studied, and the success in tracing this group prompted the decision by Danbolt and his group to continue the investigation. The clinical outcome of syphilis as estimated from the sample and from the follow-up of the total material shows a relatively close agreement and adds evidence supporting the correctness of the principle set forth by Boeck, supports some of the conclusions of Bruusgaard, and fortifies the expressed ideas of modern experts in syphilology. There is no suggestion that syphilis should be allowed to pass untreated. Gjestland will publish the details in a monograph.

DIAGNOSIS OF SYPHILIS

Again the chief subject of interest in the diagnosis of syphilis is the development of the newer techniques for positive diagnosis of syphilis—the TPI test, the immune-adherence phenomenon, and the agglutination test. Although much progress has been made in this field, the ultimate has not yet been attained.

INTRADERMAL REACTION

Intradermal Reaction to Suspension of Pathogenic Treponemas (Nichols Strain) with Formol.—Gaté and his co-workers [39] describe their method for obtaining purified suspensions of T. pallidum treated with formaldehyde (formol). Injection of 2 cc. of the suspension is made in the deltoid region and is read at the beginning of the fourth day. The reaction has been proved microscopically to be a typical allergic one. Since November, 1951, the authors have made 317 such tests on human beings. There were 211 patients known to have syphilis and 105 patients with other diseases or healthy. The reaction proved to be specific for syphilis. It was negative in primary syphilis and seldom positive in secondary syphilis. It was positive in all forms of tertiary syphilis and congenital syphilis but was inconstant in neural syphilis and latent syphilis that had not been treated. The reaction may remain positive in persons whose disease has been successfully treated, especially if they are still serologically positive. The formaldehyde-treated treponeme suspension can be used in patients suspected of having cutaneous tertiary syphilis because of the clinical aspect of their lesions, for negative reaction excludes this form of the disease and a positive reaction confirms the suspicion, provided there are no other visceral localizations of syphilis. The reaction can also be used with certainty in patients suspected of primary syphilis, since, if it is positive, it excludes a chancre in favor of the diagnosis of latent serologic syphilis with ordinary mucous lesions. Useful, but not absolute, information may be obtained from the reaction in three types of cases. 1. In a patient suspected of congenital syphilis with negative serologic reaction, a negative reaction is a big argument against this diagnosis and a positive reaction confirms it. 2. In a patient suspected of having cardiovascular syphilis, on the basis of a positive blood serum and the appearance of clinical signs, a negative reaction is a strong argument against the syphilitic origin of the cardiovascular symptoms. 3. In a patient with neural syphilis, the reaction can be followed

over a period of time to detect its eventual change from negative to positive and thus measure the efficacy of treatment. The test cannot be counted on to detect syphilis in the first place. A negative reaction does not always mean that syphilis is not present, and a positive reaction does not always correspond to an evolving case. It has not shown itself to be consistently positive in syphilis except in the tertiary and cardiovascular groups. It cannot be used as a criterion of cure.

Serodiagnosis

The serodiagnosis literature continues to describe further experience with cardiolipin antigen in various tests. Also, the problem of biologic false reactions is still of interest, in spite of indications that sooner or later we will have a procedure which will with certainty enable the physician to determine the verity or falseness of a given serologic result. Many of the problems still current are discussed briefly by Carney [40] and by Reddy.[41] Vogelsang,[42] in viewing current complement-fixation and flocculation tests using phosphatidic acids, cardiolipin, or sitolipin in the serodiagnosis of syphilis, points out that, even with the help of the new antigens, false-positive reactions showing a preference for certain definite morbid conditions nevertheless occur. Of the various methods which have been devised to distinguish false positive reactions from specific positive reactions the T. pallidum immobilization (TPI) test has attracted most attention. In the serum of syphilitics there are antibodies which, in the presence of complement, have an immobilizing action on the treponemes, and several studies of the various factors influencing this immobilization have been undertaken. The active antibodies in the reaction differ from the syphilitic reagins which react with the lipoid antigens. The TPI test is well suited to further investigation of the problems of immunity in syphilis. T. pallidum shows a tendency to spontaneous agglutination, and by means of another new test—T. pallidum agglutination (TPA)—the agglutination of T. pallidum in syphilitic sera can be greatly increased by the addition of fresh steer serum. In this way, the presence of syphilitic antibodies can be demonstrated in two hours. It is necessary, however, to submit this reaction to a series of further tests before it can be adopted as a routine measure, but if its reliability can be proved this procedure will undoubtedly offer great advantage over the methods usually employed.

Dr. William A. Hinton.—In a general discussion of serology it is worthy of note that Dr. William A. Hinton, one of the "greats" in American serology, retired Dec. 31, 1953,[43] as director of the Wassermann Laboratory of the Massachusetts Department of Public Health. He had been director of the laboratory since 1915. From the beginning, experimental work on the serology of syphilis was almost continuously a part of the laboratory. As a result of research "a glycerol cholesterol agglutination test" was devised in 1927. Since 1936, evaluation of serologic tests for syphilis conducted by the Public Health Service have shown that the Hinton test, with one exception, has been more sensitive and just as specific as any of the approved tests used throughout the country. Dr. John A. V. Davies devised the Davies-Hinton micro test, which is used by all large pediatric clinics in the State. The Davies-Hinton test for spinal fluids was also devised in the laboratory and is now the routine procedure. In 1936 Dr. Hinton published a book entitled "Syphilis and Its Treatment."

Standardization of Serologic Tests for Syphilis.—At the Gade Institute, in Bergen,[44] the routine serologic testing for syphilis includes Wassermann tests, with three different antigens and three different flocculation tests; Kahn's standard reaction; Meinicke's "Klarung's" reaction, and venereal disease routine laboratory test. The technique of each test differs so in various parts of the world that there is little hope of a fair comparison of the results of each. Professor T. Vogelsang has suggested an international standardization.This is based upon evidence of the growing importance of testing for syphilis as illustrated by statistics from his own laboratory.

Unitary vs. *Plural Conception of Antilipid Antibody in Syphilitic Serum.*—Mitra and co-workers [45] set out to investigate the difference between the unitary and plural conceptions of antilipid antibody in syphilitic serum and also to determine which of the two concepts is correct. They found that their results confirm the findings of Eagle (1935) that the antibody in syphilitic serum which is responsible for flocculation and for complement-fixation with lipid antigen is one and the same substance. Its manifestations are different in the two methods owing to different test conditions.

Complement-Fixing Properties of Cardiolipin Wassermann Antigen.—Orpwood Price [46] showed that none of the three constituents of cardiolipin and cholesterol, or lecithin and cholesterol, when employed as antigens have any ability to fix complement in the presence of syphilitic sera. He showed that mixtures of cardiolipin and lecithin have limited complement-fixing properties when these components are present at suitable adjusted strengths. He found that, using the Whitechapel Wassermann technique, the most sensitive antigen to be employed is one in which the proportion of the reagents is cardiolipin 1 : lecithin 1 : cholesterol 10 to 6.

Choice of a Formula for Cardiolipin Wassermann Antigen for Use in the Whitechapel Wassermann Technique.—Orpwood Price [47] also infers that, provided the serological activities of different preparations of cardiolipin and lecithin are up to a reasonable standard, the components of cardiolipin Wassermann antigen are interchangeable and that if the antigens so made up are used at the optimum titers they will react at the same level of sensitivity. This method of standardizing the sensitivity level of Wassermann antigens has already been shown to operate in the case of ox heart Wassermann antigens (Price and Wilkinson, 1951). Furthermore, these experiments demonstrate a method by which a serologically weakly reacting component of a cardiolipin Wassermann antigen can be detected.

Cardiolipin Antigen—An Examination of Specificity.—Schmidt [48] set out to determine and compare the specificity of the Wassermann complement-fixation test, as modified by Morch, performed with unpurified antigen (WR-M) and with cardiolipin (C-WR-M), composed of cardiolipin, lecithin, and cholesterol in proportions of 1 : 5 : 17. At the same time, the specificity of Kahn's standard reaction (KR) was compared with that of the complement-fixation tests. The study was divided into three parts. Parallel examinations, using WR-M, C-WR-M, and KR were performed for (*a*) 3,565 mainly hospitalized, nonsyphilitic patients; (*b*) 1,955 nonsyphilitic pregnant women; (*c*) about 170,000 sera submitted during a four months' test period to the Serodiagnostic Department, Statens Seruminstitut. All the blood samples were examined routinely by WR-M and KR. Sera showing positive reactions in either or both of these tests were examined by C-WR-M. As a result, details are missing on those sera which were positive only in C-WR-M, but the magnitude of that figure is known from Groups *a* and *b*. The number of nonspecific reactions corresponds to a nonspecificity for Group *a* of about 0.7% and for Group *b* of about 0.5%. These figures are not significantly different; hence it must be accepted that biologically false positive seroreactions do not occur more frequently among pregnant women Group *b* than among "normal" patients Group *a*. WR-M is the most nonspecific seroreaction both for Group *a* and for Group *b*, being significantly more frequently positive than C-WR-M and KR. No difference in specificity could be demonstrated between C-WR-M and KR for Groups *a* and *b*. Among patients with diseases of the respiratory tract showing biologically false positive reactions, WR-M was significantly more nonspecific than KR. C-WR-M was not directly comparable with WR-M and KR, because it was performed only if either or both of the latter reactions were positive. The C-WR-M was therefore compared with KR for those sera which were positive in WR-M and with WR-M for those sera which were positive in KR. On these

assumptions, KR as well as WR-M proved to be significantly more frequently positive than C-WR-M, thus being more nonspecific to sera from patients with disease of the respiratory tract. A certain interdependence appears to exist between the degree of potency of WR-M and the positivity of C-WR-M and KR, respectively (rising numbers of positive reactions with C-WR-M and KR, respectively, at increasing titers of WR-M), while inadequate numbers of C-WR-M + and KR + sera presented determination of a potential interdependence of these two seroreactions. Among sera from pregnant women with biologically false positive reactions, WR-M was significantly more nonspecific than KR. C-WR-M was compared with WR-M and KR on the assumption explained above. The small number of KR-positive sera, for C-WR-M and WR-M were compared, does not allow the author to decide whether significant differences in specificity exist between the two complement-fixation tests, but in this small sample of sera there is nothing to indicate that the relation between C-WR-M and WR-M should differ from that determined for Group *b*. No differences in specificity could be demonstrated between C-WR-M and KR when their specificities for WR-M + sera were compared. The incidence of unreadable reactions in WR-M was significantly more frequent among sera from pregnant women than among sera from patients with diseases of the respiratory tract. No differences were observed in the hemolysis curves from the unreadable sera from the two categories of patients. The relation between C-WR-M and WR-M among sera with biologically false positive reactions is suggestive of the relation between the two complement-fixation tests in primary syphilis. It is suggested that the serum changes causing biologically false positive seroreactions may be very largely analogous to those occurring in primary syphilis. Schmidt [49] also studied the use of cardiolipin antigen in normal persons.

Cardiolipin Antigen—Mazzini Cardiolipin Microflocculation Test. — Bossak and his co-workers [50] have evaluated the recently evolved Mazzini cardiolipin microflocculation test by comparing its performance with a battery of other serologic tests in more than a thousand blood specimens. Cardiolipin-lecithin antigen was used in some of the batteries of tests with which the new test was compared, and lipoidal antigen in other tests. The Mazzini microflocculation test was more sensitive than any of the tests with which it was compared, but it appeared to be less specific than many of the other tests.

Cardiolipin Antigen—Specificity of Results of Kahn and Cardiolipin Tests.—Kahn and McDermott [51] state that the results of two tests with cardiolipin antigens reported by control laboratories in recent official serologic evaluations of laboratories (1949, 1950, and 1952) indicate that cardiolipin antigen tests may give large numbers of false positive reactions. In the same evaluation, the results of the standard Kahn test with Kahn antigen reported by the control laboratory were free from false positives. No change in sensitivity has been made in the standard Kahn test since the serologic conference of the League of Nations Health Organization at Copenhagen, in 1928, as it was believed that any advantage of increasing the sensitivity of the test would be temporary, leading sooner or later to a lowered specificity. The authors also discuss the great importance of official evaluation of State serologic laboratories.

Use of Some Synthetic Phosphatides in Antigens for the Serodiagnosis of Syphilis.—Tonks and Allen [52] review the pertinent literature and present a report of studies in which synthetic phosphatides were substituted for cardiolipin or natural lecithin in the preparation of antigens for the serodiagnosis of syphilis. Antigens containing the various synthetic substitutes have been used in the VDRL microflocculation test and the Kolmer complement-fixation test. The use of pure synthetic compounds in the preparation of antigens would offer certain advantages in the standardization of serodiagnostic tests for syphilis. In addition, the investigation holds some promise of revealing the mechanism of reaction and perhaps the molecular groupings which are involved.

Quantitative Complement-Fixation Test.—Mountford [53] attempted to analyze the errors in the complement-fixation reaction due to high concentration of serum, but these were not found to be due to any one factor. Heating to 56 C. for 30 minutes reduced the anticomplementary effect of the serum without altering the antibody content. Heating to a higher temperature (62 C. for 15 minutes) produced the same results.

Observations on Optimal Zone Reaction and Seroresistance.—Cannefax [54] has presented a study of the optimal zone procedure, which is claimed by Kahn to have prognostic significance in the early determination of seroresistance following adequate antisyphilitic therapy. In this procedure 10 serum antigen rations are employed, and a so-called pattern is developed as the result of difference in the degree of reactivity of syphilitic sera with the different serum antigen ratios. Cannefax studied the optimal zone pattern of 300 seroresistant patients and found these patterns to depend primarily upon reagin concentration. He concludes that the optimal zone procedure does not appear to produce information concerning seroresistance that is not already obtainable with the more easily performed standard quantitative serologic test for syphilis performed at regular intervals.

Effects of Certain Temperatures and Time Limits on the VDRL Slide Text.—Cannefax and his co-workers,[55] in addition, studied the effect of variations in temperature on the VDRL slide test. They found that the sensitivity of the test increases as the temperature of the serum being tested is increased, regardless of the temperature of the antigen when prepared or used. The sensitivity of a given antigen suspension increases as the temperature at which it is used decreases. Conversely, antigen sensitivity decreases as the temperature at which it is used increases. The most sensitive antigen suspension is that prepared with warm reagents and employed at a colder temperature than that at which it was prepared.

Clarification of Syphilitic and Nonsyphilitic Serodiagnostic Reactions.—In another study of the universal serologic reaction, Kahn [56] attempts to use it to clarify the behavior of serodiagnostic reactions employed in the diagnosis of syphilis. The universal reaction, present in health, is intensified in disease. He states that a positive serodiagnostic reaction, whether it occurs in syphilis, in nonsyphilitic diseases, following irradiation, or following injection of various substances, is the result of tissue breakdown or of increased tissue catabolism over the normal level and that the antibodies produced to the lipids liberated are of such a nature and concentration as to be detectable by means of serodiagnostic tests. This concept lends support to the clinical significance of positive serodiagnostic reactions in the absence of syphilis. False positive serodiagnostic reactions may be encountered (1) concurrently with pathological processes or increased tissue catabolism, (2) for weeks or several months after recovery, (3) prior to the appearance of clinical manifestations in diseases of prolonged onset, and (4) in normal persons (rarely).

Pseudosyphilitic (Wassermann-Positive) Virus Pneumonia.—Between 1940 and 1952 Herzog and Pulver [57] observed 37 patients with pneumonia in whom the result of the Wassermann reaction was transiently positive. All but three of the patients had fever lasting 7 to 10 days, the illness beginning in most cases with general symptoms rather than those of respiratory tract infection. In 2 cases there were no symptoms at all, while in 15 there were signs of diffuse bronchitis; in 16, of pneumonia, and in the remaining 4 cases there were no abnormal signs in the lungs. The roentgenographic abnormalities consisted of ill-defined areas of mottling of various sizes, which usually disappeared in three to five weeks; in four cases the hilar shadow was enlarged. The positive Wassermann reaction was usually obtained three to four weeks after the roentgenographic abnormalities had cleared up. The presence of cold agglutinins was not demonstrated. There were no abnormal physical signs in the nerv-

ous system, but of 15 cases in which lumbar puncture was performed in 3 some abnormality was found in the cerebrospinal fluid. The authors believe that in these cases the pneumonia was due to a virus. Similar cases have previously been reported as "pseudoluetic perihilar bronchopneumonia" and "Wassermann-positive lung infiltrations." Editorial comment by the *British Journal of Venereal Diseases* states that

> the cases described in this paper seem to differ from other cases of pneumonia only in having a transiently positive Wassermann reaction, but this has been recorded in many diverse febrile illnesses. There is no convincing evidence that the condition was due to a virus. To describe it as a new disease entity hardly seems justified, and may be misleading.

Studies on the Comparative Behavior of Various Serologic Tests for Syphilis.—The records of 100 patients with primary and 100 patients with secondary syphilis were reviewed by Cutler, Chester, and Price,[58] in an effort to determine the rate and pattern of return to seronegativity following treatment with penicillin, as measured by a battery of seven standard serologic tests for syphilis utilizing crude lipoidal antigens. All of the patients were treated for their first infection. Following treatment, patients with primary syphilis returned to seronegativity much more rapidly than did those with secondary syphilis. More sensitive tests, such as the Kline exclusion and Mazzini tests became negative more slowly than did the less sensitive tests. This was noted particularly in patients treated for secondary syphilis. Transient seropositivity occurring after the patient had become seronegative was seen quite frequently, and it was established that this did not signify relapse or reinfection, inasmuch as the patients again returned spontaneously to seronegativity. A variety of individual patterns of serologic response to infection and successful treatment were found which were at variance with the usual patterns. The most interesting and important part of this paper is the detailed reporting of two patients with dark-field positive early syphilis who had been observed for many months prior to infection because of biologic false positive serologic tests. Each of these patients showed repeated low titer, positive S. T. S. before infection, and an increase in titer at the time of infection. One patient became completely seronegative, one almost completely seronegative, 1,000 days after the institution of treatment. The authors point out that these cases demonstrate that a biologic false positive S. T. S. does not render the individual immune to infection by T. pallidum.

VDRL Tube Test—Comparison with the Kahn and Kolmer Tests for Syphilis.—Djanian [59] tested 8,228 sera in parallel using the VDRL tube flocculation test and the standard Kahn reaction in order to compare the sensitivity of the two tests. In addition, 746 of these sera were subjected to the Kolmer complement-fixation reaction. No attempt was made to evaluate specificity. There was complete agreement in the results of both the DRL and the Kahn test in 7,840 sera out of 8,228 (95.3%). Of the 388 sera in which the results did not agree, 36 were positive with the VDRL test, 25 of these being doubtful and 11 negative with the Kahn test. Of the remaining 352 sera which were negative with the VDRL test, 138 were positive and 214 doubtful with the Kahn test. One hundred two more sera gave positive results with the Kahn test. If the doubtful results are considered positive, the positive results rise to 341 (an increase from 1.2 to 4.1%). When 746 sera were tested in parallel with WDRL, Kahn, and Kolmer procedures, there was total agreement with 608 sera (81.5%) and disagreement with 138. The sensitivity of the three tests in these 746 sera was Kahn, 39.8%; Kolmer, 26.7%, and VDRL, 25.6%.

Agglutination of T. Pallidum in Syphilitic Serums.—In investigations carried out in the Venereal Disease Experimental Laboratory of the U. S. Public Health Service, at the University of North Carolina, McCleod and Magnuson [60] have confirmed Tani's observation that treponemes killed with antiformin do not undergo spontaneous agglutination and are agglutinated by syphilitic sera and have shown that this agglutination is enhanced by the conglutinin present in beef

serum. Suspensions were also made of treponemes killed by exposure to a temperature of 56 C. for 40 minutes, to oxophenarsine (1:4,000), to 0.2% phenol, or to 0.1% formalin. No spontaneous agglutination was seen in suspensions prepared by the first two methods, but it occurred to some extent in phenol-killed suspensions, while the formalin-killed suspensions failed to agglutinate altogether. The treponemes were obtained by extraction with saline solution from the testes of rabbits infected with the Nichols strain of T. pallidum 7, 9, 11, or 13 days previously. When fresh beef serum was used as a source of complement in the treponemal immobilization (TPI) test, complete disappearance rather than immobilization of treponemes was found to occur, and tests for residual complement showed conglutination to be present. No immobilizing antibody could be demonstrated when heated beef serum was used. Quantitative tests on a syphilitic serum using beef and guinea-pig serum as sources of complement showed that the "disappearance titer" with the former was similar to the immobilization titer with the latter. Disappearance also occurred when the living suspension was heated to 56 C. for 40 minutes and the tests incubated either aerobically or anaerobically. It was later found when washed killed suspensions were used that disappearance of treponemes always occurred with fresh beef serum, while agglutination took place when heated beef serum was used. When the serum was suitably diluted these effects were overcome, while sufficient conglutinin activity remained to enhance the agglutination of the treponemes by syphilitic sera. For test purposes 0.1 ml. treponeme suspension (heat-killed), 0.1 ml. fresh beef serum diluted 1:7, and 0.1 ml. of the inactivated serum under test were mixed and shaken at 37 C. for two hours and the degree of agglutination read under the high power of the microscope. With this technique the test showed good reproducibility. The titer of a pooled positive serum examined on 24 occasions with six different suspensions varied between 1:40 and 1:160. Sera from 154 presumably nonsyphilitic persons were examined; the TPI test was negative in all cases; the agglutination test was negative in 150, positive in 1, and doubtful in 3. With 12 sera from patients with primary syphilis the standard serum tests gave 8 positive and 3 negative results (1 serum was not tested); the TPI test gave 5 positive and 6 negative results (1 serum showing nonspecific immobilization), and the agglutination test gave 10 positive and 2 negative results. All three tests gave positive results with 66 sera from patients with secondary syphilis and with 33 sera from patients with latent syphilis. Quantitative tests showed no correlation between the titers given by the three tests, although in general the agglutination titers were higher than the immobilization titers.

Immune-Adherence Phenomenon. — Nelson [61] reviews the literature on previous studies designed to demonstrate phagocytosis of virulent T. pallidum in vitro. In these studies observations on control preparations led to a recognition of an immunologically specific reaction between normal human erythrocytes and treponemes sensitized with antibody from syphilis serum. The reaction required a heat-labile substance in normal serum, presumably complement (C′). Although not definite, the experiments suggested that this reaction was an essential precursor to phagocytosis of the treponemes by human leucocytes. In the present paper the author describes various experiments which provide additional data on the reaction of T. pallidum with erythrocytes and demonstrates that a similar reaction occurs with other micro-organisms, e. g., Diplococcus pneumoniae, Shigella paradysenteriae, Salmonella typhosa, Micrococcus aureus, and Mycobacterium tuberculosis. It is also shown that the union of sensitized organisms with erythrocytes, hereafter termed the immune-adherence phenomenon, leads to an enhancement of phagocytosis. The observation that erythrocytes play a role in an immunologic reaction with organism, antibody, and C′ offers advantages to studies on the in vivo resistance of the host to infection and also may lead to the development of clinical diagnostic procedures involving the use of prepa-

rations of erythrocytes and micro-organisms for the detection of circulating antibody. Olansky and his group [62] studied the reactivity of the immune-adherence (IA) test on 71 presumably nonsyphilitic patients and 234 patients with syphilis diagnoses. They also discussed the relative reactivities of IA, TPI, and VDRL slide tests for syphilis in 305 previously diagnosed patients. The pattern of the IA test more closely follows the TPI test than that of the VDRL slide test. Since the antibodies that produce positive reactions in the TPI and VDRL slide-type tests are known to be different, the substance producing such reactions in the IA test is similar if not identical with the substance that activates the TPI test. If this conclusion is correct, then the positive reactions in the IA test may be reflective of past rather than of present syphilis infection. Because the IA test is a simple rapid laboratory procedure, since antigen for this test need not be freshly prepared, this test may be a practical substitute technique for detecting the TPI antibody.

Treponemal Immobilization Test. — The newer procedures with possibilities in the diagnosis of syphilis—the agglutination test and immune-adherence phenomenon briefly described above—are still not fully evaluated. The treponemal immobilization test (TPI) was given so much space in the last review that the present account needs only to list the newer sources of information, the papers dealing with the further world-wide experiences with the procedure, comparisons with other "verification" tests, newer technical suggestions, and criticisms of the test.

Meinicke [63] has described in a letter the symposium on the TPI test held in Marseilles. Beerman [64] has presented an extensive review of the literature on this procedure. The details of this presentation were covered largely in the preceding annual review of syphilis. Miller and his co-workers [65] reported their further experience with this test. They stress the fact that, great as its value is as a diagnostic test, the treponemal immobilization test cannot be used as a guide to treatment. This is apparent, because no amount of treatment appears to alter the treponemal immobilizing test in patients with syphilis not adequately treated early in the infection. The amount of treatment for syphilis to be given must be based on accepted standards of adequacy. In this situation the serologic test may be of more value, as there is a tendency for it to become negative in response to treatment.

The treponemal immobilization test is the only practical procedure available for separating the group of false positive reactors from patients with latent syphilis. Here the treponemal immobilizing test is of inestimable value, both in curbing the tendency to make a diagnosis of false positive reactions too easily and to prevent the psychic trauma produced by the erroneous diagnosis of syphilis.

The treponemal immobilizing test on the spinal fluid is of great value as a diagnostic test for neurosyphilis. Unlike the serologic tests, it remains positive indefinitely, regardless of the amount of treatment, unless given quite early in the course of the disease, in both symptomatic and asymptomatic neurosyphilis. In the experience of these authors, it was positive in the spinal fluid of all persons with tabes dorsalis but negative in cases of latent syphilis.

Miller's group collected evidence to establish the fact that the antibody responsible for the treponemal immobilizing test passes the placental barrier, as has been established for reagin. This passive transfer of antibodies to nonsyphilitic offspring from syphilitic mothers is of great practical importance. They found that the serologic test reagin disappeared by the third month in 91% of their patients. However, the immobilizing antibody persisted to the fourth or fifth month, usually disappearing by the sixth month. It is interesting to note that the duration of the persistence of this antibody parallels that of other passively transferred antibodies, such as that of herpes simplex. This longer persistence of the immobilizing antibody as compared to that of reagin must be remembered when evaluating the status of these babies. These references will be of value to the interested reader to obtain further data

on experiences with the test in a number of countries of the world. In general, the conclusions are qualifiedly favorable to the procedure.*

Comparison of Results Obtained by the T. Pallidum Immobilization Test and the Kahn Verification Test: In Dr. Reuben Kahn's own bailiwick, at the University of Michigan Hospital, Harrell [83] has carried out comparative study of the treponemal immobilization test and the Kahn verification test. Serum from 48 patients, who on the basis of clinical diagnosis probably had biologic false positive serologic tests, was subjected to both tests. Twenty patients had positive results in the treponemal immobilization tests (TPI). In 70% of these, there was agreement with the Kahn verification test; in 30%, disagreement. Twenty-eight of the total number had negative TPI results. Agreement with the Kahn verification test existed in 64.3%; disagreement, in 33.7%. The discovery, many years ago, by Scott and his collaborators (Scott, V. C.; Rein, C. R.; Schamberg, I. L.; Moore, J. E., and Eagle H.: The Serologic Differentiation of Syphilitic and False Positive Sera, *Am. J. Syph.* **29**:505, 1945) that the result of the Kahn verification test depends in large part upon the reagin titer was confirmed by this study. The Kahn titer was markedly higher in the present study in those sera which gave a "syphilitic type" of verification than it was in those in which the "biologic false positive type" was found. This was true regardless of the results of the TPI test. The author concludes "these data confirm the clinical experience of many syphilologists that too much reliance should not be given to the results of the Kahn Verification Test."

Comparison of the Neurath and T. Pallidum Immobilization Procedures: Roy and his co-workers [84] compared the treponemal immobilization test (TPI) and the Neurath euglobulin inhibition test in 96 patients, some of whom had syphilis and some of whom did not. Complete agreement was found between the two tests in 67.7% of the patients, and complete disagreement occurred in 11.5%. The Neurath test was in agreement with the clinical diagnosis in 64.5% of the cases, not in agreement with the diagnosis in 16%, and of no value in relation to diagnosis because of inconclusive or variable results in 19%. In sharp contrast, the TPI test was in agreement with the clinical diagnosis in 95.7% of the cases, not in agreement in 4.3%. In a study of the suitability of test tubes for collection of specimens for the TPI test, standard vacutainer tubes proved unsatisfactory but special sterile vacutainer tubes were satisfactory. The authors concluded that there was a much closer correlation between the TPI test and clinical diagnosis than was found between the Neurath test and clinical diagnosis.

Technical Modification of the TPI Test: Several reports dealing with technical modification of the TPI test were published during the past year (Delacretaz,[85] Meinicke,[86] Greifelt and his colleagues,[87] Nielsen, [88] and Portnoy and co-workers [89]). In order to eliminate inconclusive results in the treponemal immobilization test, Nielsen [88] recommends altering the medium to contain four times the concentration of sodium thioglycollate (Difco) prescribed by Nelson. So far no bad influence of the increased amount of sodium thioglycollate has been observed. Portnoy and his associates,[89] in the Venereal Disease Research Laboratory, Chamblee, Ga., report a number of difficulties in the performance of treponema immobilization tests, which include poor survival of the treponemes with a consequent high incidence of inconclusive findings, the occurrence of false positive reactions in known negative sera, and lack of reproducibility of the test on retesting. They had previously reported that increasing the concentration of sodium thioglycollate improved treponemal survival time. The current studies detail their efforts to improve the reproducibility of the test. It was found that

* References 66-82; Thivolet, J.[83]; Floch, H.; Rolland, M., and Sohier, R.: Étude des T.P.I. chez les lépreux, in Charpy,[16] pp. 221-223; Gaté, J.; Sohier, R.; Thivolet, J.; Saucaz-Larame, M.; Bénazet, F., and Rolland, M.: L'evolution du T.P.I. dans les syphilis traitées, in Charpy,[16] pp. 225-241.

the test is more sensitive when treponeme concentration is low. No evidence of "sensitization" in vivo of the treponeme by antibodies produced in the rabbit was found when rabbits with orchitis of more than 48 hours' duration were used.

Critique of the TPI Test: Kolmer and his group have been among those more critical of the TPI procedure. His paper with Lynch [90] and the correspondence with Nelson [91] are to this point. Kolmer and Lynch state that false positive and doubtful serologic reactions in syphilis are frequently due to technical errors or the use of faulty reagents and therefore are largely preventable. Biologic false positive and doubtful reactions may occur with serums of normal healthy persons and those with various nonsyphilitic diseases or conditions. In national surveys on serologic evaluation from 1935 to 1950, the author-serologists, employing their own lipoid antigens, reported an incidence of 0.1% (1:1,000) to 0.97% (about 1:100), averaging 0.47% (about 1:200), false positive and doubtful reactions with serums of normal, presumably nonsyphilitic, donors. In the national surveys on serologic evaluation from 1946 to 1950 the author-serologists, employing cardiolipin antigens, reported 0.16% (about 1:630) false positive and doubtful reactions with serums of normal, presumably nonsyphilitic, donors. The true incidence of biologic false positive and doubtful serologic reactions with the serums of donors with various nonsyphilitic diseases and conditions is still unknown. The results of mass serologic surveys, however, indicate that it is higher than hitherto surmised. The antibody or reagin responsible for biologic false positive and doubtful serologic reactions is apparently identical or closely related to the Wassermann antibody or reagin occurring in syphilis and other treponemal diseases. This antibody or reagin is separate and distinct from agglutinins and complement-fixing and immobilizing antibodies for virulent T. pallidum occurring in syphilitic serums. So far, the immobilizing antibody has not been observed in the serums of normal persons, but it has been found in the serums of some persons giving biologic false positive serologic reactions due to various nonsyphilitic diseases. The test for immobilization of T. pallidum is not yet ready for general adoption and use. Its practical value in differentiating between true positive serologic reactions due to latent acquired or congenital syphilis and biologic false positive and doubtful serologic reactions remains to be determined. In spite of the criticisms of this procedure, Canada has seen fit to extend a TPI test service, begun in 1951, to all Provinces of that country.[265]

Cerebrospinal Fluid

Spirochetal Antigen Agglutination Test.—Roemer and Schlipköter [92] used a spirochetal antigen produced by Bering Werke Marburg. A drop of this antigen is added to 0.2 ml. spinal fluid in a test tube. This is kept at 37 C. in the incubator for three hours and then at room temperature until the next day. In positive cases, marked flocculation is microscopically discernible. The spirochetal agglutination test yields results comparable to those of the Wassermann and the Meinicke tests.

Protein "Patterns" of Cerebrospinal Fluid in Different Stages of Syphilis Before and After Therapy.—Flodén [93] found that in the various phases of syphilis cerebrospinal fluid protein changes, on the whole, follow regular "patterns." He also found that after adequate therapy there is a reversion towards protein conditions of a type similar to that which has been found in material of healthy persons. Total protein determination alone is too crude a method for registering even considerable changes in the protein pattern, which can be clearly demonstrated only if the globulins and albumins are also determined.

Iatrogenic Meningitis.—In a review such as this one, concerning a disease which demands a cerebrospinal fluid examination in every case prior to definite disposition, the subject of iatrogenic meningitis should be mentioned. According to the Cutlers,[94] this disease is increasing. They review the subject along with their report of two cases which resulted from lumbar puncture for

spinal anesthesia. The same syndrome can follow lumbar puncture for diagnosis, as is so often performed in the diagnosis and treatment of syphilis. The causative organism in most cases of iatrogenic meningitis is Pseudomonas aeruginosa. Effective therapy depends on proper identification and sensitivity tests of the organism involved.

CLINICAL MANIFESTATIONS

Clinical syphilology continues to be a field for fruitful research. The discovery and rediscovery of unusual manifestations is a tribute to the protean nature of this infection. The studies on fatal syphilis from Great Britain are a grim reminder that syphilis is still an important cause of death. The relationship of syphilis and cancer of the cervix has been of great interest in the past, but no definitive study had been produced. A controlled investigation of this relationship has exonerated syphilis as such as the cause of cervical cancer, although indirectly, in the past, through therapy syphilis contributed to the development of cervical cancer. Syphilis in pregnancy and congenital and ocular syphilis are other fields in which new facts of a clinical nature are being disclosed. The most striking phenomenon, however, is the relatively large number of papers dealing with rupture of syphilitic aneurysms into various viscera. Indeed, syphilis is far from dead.

FATAL SYPHILIS

Fatal syphilis has been the subject of three studies and an editorial in the *British Journal of Venereal Diseases* (editorial,[95] McElligott,[96] Ross,[97] and Newcomb [98]). After a careful statement of the known facts about syphilis as a cause of death, McElligott [96] tabulates figures from the clinics in England and Wales and from the Registrar General's Reports. His Table I shows cases of acquired syphilis of less than one year's duration attending the clinics for the first time. Following are noteworthy points: (*a*) the steady fall in both male and female new cases down to 1939; (*b*) the steep rise up to 1946, which would be even steeper if service cases had been included; (*c*) the rapid fall in both male and female cases down to 1950, which is continued in 1951, to a record low level, in spite of the reentry into civil life of large numbers of young men from the services. The female-male ratio of patients treated has progressively improved since 1931. Table I also shows cases of acquired syphilis of more than one year's duration attending the clinics for the first time. There is a comparatively slow fall in male new cases and an actual rise in the female cases, due doubtless in some part to the growing practice of routine antenatal blood testing and the referring of positive cases to clinics. It is also likely that an increasing awareness of late and latent syphilis may be at work among general practitioners.

Table II shows deaths from general paralysis of the insane, tabes dorsalis, and aneurysm of the aorta (including service personnel). Deaths from aortic aneurysm in males show little significant change, and the female death rate seems to be rising fairly consistently. It is of interest that of 642 male and 433 female deaths in 1950, the aneurysms in no less than 212 males and 208 females were certified as nonsyphilitic. It is uncertain to what extent, if any, "compassionate" certification is responsible for this high proportion. These figures are especially interesting in view of the often-quoted opinion that aortic aneurysms are four times as common in men as in women. The increasing number of deaths in women would seem to suggest that a far smaller proportion of women than men have been treated in the early stages of infection.

The recent dramatic fall in deaths from parenchymatous neurosyphilis is probably due to the introduction of more effective and less dangerous methods of treatment, e. g., penicillin in general paralysis of the insane and sulphonamides in the infected atonic bladder of tabes. Also, the growing practice of routine diagnostic lumbar puncture in late and latent syphilis must have led to the diagnosis, treatment, and cure of many cases of neurosyphilis while they were still in the asymptomatic stage.

Table III shows deaths from disease of the aortic valve without mitral disease between the ages of 35 and 80 in 1938 and 1949. The reason for the consistent fall in all age groups is difficult to understand, particularly in the age group 55 to 70, where syphilis might reasonably be assumed to be responsible in a fairly high proportion of cases. Table III also shows deaths from aneurysm of the aorta between the ages of 35 and 80 in 1938 and 1949. There is a consistent fall in all the age groups over the 11-year period. The numbers considered to be syphilitic by the certifying doctors are not known. In 1939, 770 men and 341 women were certified as having died from other forms of syphilis, and in 1949 these numbers had fallen to 454 men and 208 women.

Table IV shows deaths per thousand live births of infants under one year certified as due to congenital syphilis. There was a steady fall in the rate, except during three of the war years, and this fall continued during 1945 to 1947, the period of highest incidence of early infectious syphilis.

Though it is difficult to compare the Registrar General's figures with those estimated by the U. S. Public Health Service, it seems likely that the over-all fall in mortality from syphilis in the United States has been paralleled by at least as steep a fall in Great Britain.

The lethal hazards of untreated syphilis, considerable as they are, are not so great as is popularly supposed, and in the patient who is properly and fairly promptly treated lethal hazards are minimal. The legacy of undetected syphilis, especially among women, that follows a war is bound to be large, and at the end of the first world war there were many gloomy warnings about the fate of those who were treated as well as of those who escaped treatment. These prophecies were never fulfilled.

Today the number of new infections has reached a record low level and, with continued peace-time conditions and vigilance at the ports (the link with the vast reservoirs of infection overseas), the outlook for the future should be good. Meanwhile, the death rate from syphilis for the next few decades will depend largely on the discovery and treatment of the thousands who must still be at large in the as yet asymptomatic stages of disease. The tracing of contacts in the early infectious stages is not enough. Fathers and mothers as well as brothers and sisters of congenital cases must be clinically and serologically investigated, as should be the spouses and children of all whose blood tests are found to be positive. Though this in some cases may reopen old wounds and cause distress, it may often enough be the life-saving measure, and it is sometimes the doctor's duty to risk the unpopularity that insistence of such investigations may entail. According to Ross,[97] tables compiled from material obtained from a special report form (for use by local hospitals, issued by the Hospital Committee of the Local Authority responsible for administration of the large Poor Law hospitals in its area) of deaths from syphilis demonstrate the preponderance of male patients and institutional certifications, the relative proportions of deaths from neurosyphilis and vascular syphilis, the possibility of erroneous certification in known syphilitics, and the hazards of malarial and intravenous therapy. Attention is drawn to the diminishing numbers of deaths from parenchymatous neurosyphilis and more especially from aneurysm since 1940. The tendency of untreated syphilitics to die from syphilis at an earlier age than normal and the absence of cases treated early, except in one instance, is observed. Newcomb[98] has shown the trend of syphilis in the postmortem room at St. Mary's Hospital for the last 30 years. The incidence now is remarkably small, and it is wondered whether in 30 years' time it will have become impossible to find the stigmata of syphilis at necropsy.

EARLY SYPHILIS

Chancriform Pyoderma. — Laymon, Balogh, and Dixon[99] present two cases of chancriform pyoderma, one of the penis and one of the face. They point out that this is an unusual type of pyogenic skin infection characterized by superficial indurated ulcera-

tion with regional lymphadenitis. Syphilis, tuberculosis, accidental vaccination, chancroid, tularemia, impetigo, cutaneous diphtheria, milker's nodules, and granulomas following injuries in swimming pools may clinically simulate this condition and must be differentiated by appropriate laboratory methods. The diagnosis must be made by exclusion, as cultures usually show only banal pyogenic organisms.

Penile Ulceration in Infectious Mononucleosis.—Kallos [100] reported an unusual case of infectious mononucleosis in a 20-year-old white youth, who presented himself with a painful ulcer on his prepuce and tender large inguinal nodes. In addition he had a fine erythematous papular eruption over the chest and abdomen. The diagnosis of infectious mononucleosis was made from the peripheral blood picture and was confirmed by a heterophile antibody test, which proved to be positive in a high dilution, 1: 7,168. It is certainly unusual for infectious mononucleosis to start on the genitalia with an ulceration which might be mistaken for primary syphilis.

Acquired Syphilis in Children.—Rees [101] has reported six cases of acquired syphilis in children and one possible reinfection. All of these occurred during the seven years 1946 to 1953, during which 10 new cases of congenital syphilis in children of 14 years and under and 45 cases of primary and secondary syphilis in adult females were diagnosed. These findings suggest the need for routine examination and follow-up of the familial contacts of patients with early infectious syphilis.

LATENT SYPHILIS

Syphilis in Would-Be Blood Donors.—In the spring of 1952 the Swedish Red Cross organized a drive for blood donors in the County of Malmöhus, with the result that 5,908 new donors were registered.[102] Among them were 4,009 who were willing to serve not only in wartime but also in peacetime. The typing of these prospective donors was undertaken at the blood donor center of the Malmö Hospital, while the pathological-bacteriological department of the same hospital undertook the search for cases of syphilis. In *Svenska läkartidningen,* April 17, 1953, Dr. Bengt Willert and Dr. Sten Winblad have published their findings of 5,668 would-be donors and their experiences with regard to the elimination of persons with syphilis from among them. After the first 460 examinations had been carried out with Meinicke's reagent for screen testing, it became evident that this was not enough by itself. In addition to this test, a complement-fixation test with cardiolipin as antigen was carried out, and, in doubtful cases, multiple tests were carried out next day with Meinicke's, Kahn's, and complement-fixation tests. Altogether 5,636 samples of blood were examined for syphilis. A slight Meinicke reaction was observed in 145 cases, and a definitely positive Meinicke reaction, in 54 cases. Thirteen persons had a positive Wassermann reaction, but there were only eight cases (1.4 per thousand) in which the reaction was positive to all three tests, Wassermann, Meinicke, and Kahn. There were five cases in which the Wassermann test was positive, while the other tests were negative. Dr. Willert and Dr. Winblad have come to the conclusion that, in searching for syphilis among prospective blood donors, screening with only one test is not sufficient for the purpose. At least two tests are needed, and one of them should be a complement-fixation test according to the Wassermann technique.

LATE SYPHILIS

Gumma of the Breast.—Whitaker and Moore [103] reported a case of gumma of the breast.

Syphilitic Mediastinitis.—Few authentic cases of mediastinal syphilis have been reported, because of its great rarity and partly because of difficulty in diagnosis. Leather [104] recorded in detail the case of a 54-year-old woman in whom the presence of syphilis was amply confirmed by the strongly reactive serologic tests for syphilis and the presence of gummata on the forehead and below the

jaw. Moreover, her general condition was clearly due to superior mediastinal obstruction—a livid, swollen face, cyanosis and intense dyspnea, stridor and paroxysmal brassy cough, gross venous engorgement—and she responded dramatically to antisyphilitic treatment. It therefore seemed reasonable to Leather to assume that gummatous mediastinitis was the cause of her illness.

Tertiary Syphilis of Female Upper Generative Tract.—Lawlor and Rodan [105] reported at length a case of tertiary syphilis involving the fundus uteri, both Fallopian tubes, the right ovary, and the broad ligament of the right side, with penetration into the vagina. Hysterectomy and bilaterial salpingo-oöphorectomy were formed after antisyphilitic treatment, enabling the reporters to give a full description of the lesion.

Interrelation Between Uterine Cancer and Syphilis.—Røjel [106] made an exhaustive statistical investigation of the incidence of syphilis in patients with uterine carcinoma compared with the incidence in suitable controls. The clinical material consisted of 1,438 patients with uterine carcinoma treated at the Radium Centre, Copenhagen, during the period 1938-1945. In addition, 1,398 controls were checked with the syphilis register and police files of prostitutes in the same manner as the cancer patients. The author made the following conclusions: 1. Syphilis occurred with the same frequency in all strata of society in his patient and control series. 2. Syphilis was commoner among patients with cervical carcinoma than among controls of same age distribution, social level, and domiciles. 3. The incidence among prostitutes, who have the highest frequency of syphilis, was the highest in the lowest strata of society. 4. Even the exclusion of the prostitutes did not affect the preponderance of syphilis among patients with cervical carcinoma. In the author's opinion, it does not appear unreasonable to assume that arsenical compounds, such as arsphenamine, constitute the carcinogenic factor in carcinoma of the uterine cervix and of the tongue in syphilitic patients.

SYPHILIS OF BONES AND JOINTS

The 10th review of rheumatism and arthritis [107] is concerned with the literature published from 1946 through 1950. In the section on arthritis due to specific infectious agents are reviews on gonorrheal arthritis, syphilitic arthritis and synovitis, and yaws.

Putkonen, Teir, and Pyörälä [108] present four patients with juxta-articular nodes. All had syphilis previously untreated; three had a node in the region of the great trochanter on both sides, and in two of them this was the only site of occurrence. In three cases the histologic picture was identical: an outer fibrous zone composed of coarse collagenic fibers, an intermediate zone of granulation tissue, a central area of necrosis. In the fourth case this division into zones was not present, and the histological appearance was also in other respects nonspecific. The syphilitic etiology of these formations could not be established on the basis of the histologic picture alone. The nodes were observed to regress or disappear in all cases after antisyphilitic treatment. Three patients received only penicillin, while one had both therapeutic malaria and penicillin. Syhpilitic juxta-articular nodes are evidently not so unusual as is generally assumed. The four cases were noted in the course of one year among a total of 95 patients with previously untreated acquired syphilis. In this series there were 44 cases of neurosyphilis, but this apparent association of juxta-articular nodes and neurosyphilis may be merely coincidental.

Charcot's Joints in Diabetes Mellitus.—Sheppe [109] has reported the development of lysis and absorption of the metatarsal and phalangeal bones in the right foot of an obese female diabetic. These changes are believed to be secondary to a proved diabetic neuropathy and are comparable to those occuring in other diseases producing neurophatic joint lesions.

Significance of Growth in Roentgenological Skeletal Changes in Early Congenital Syphilis.—From an examination of the roentgenograms and the history in 59 cases of infantile congenital syphilis at the Univer-

sity Hospital, Oslo, Engeset, Eek, and Gilje [110] concluded that the typical changes in the skeleton are due to growth disturbances rather than to the presence of active syphilitic tissue in the bones; further, that such changes are not synonymous with the presence of active syphilis. They point out that from the width of the zones of rarefaction and the position of the growth lines and newly formed subepiphyseal normal spongiosa the time of onset of the growth disturbance can be deduced and the duration of effective treatment of the mother determined. The periosteal changes are probably largely due to growth disturbances and secondary traumatic influences. These observations do not, however, apply in cases of late congenital syphilis. It is suggested that since the early bone lesions usually heal without leaving a scar or deformity they are unlikely to be due to destructive inflammatory lesions. The authors state in conclusion that "while no irrefutable proof has been offered of the bone changes in infantile congenital syphilis consisting of syphilitic granulation tissue . . . the designations syphilitic endochondritis, diaphysitis, and periostitis should be abandoned in favor, for example, of osteochondroperiostitis."

CARDIOVASCULAR SYPHILIS

Continued advancement in the clinical aspects of cardiovascular syphilis have been noted during July, 1953-July, 1954. The study by Webster and his group is especially noteworthy. Peralta,[111] one of the earliest investigators of the penicillin therapy of cardiovascular syphilis, has contributed a monograph on his further experience with this problem. In Peru cardiovascular syphilis is fourth among the causes of cardiovascular morbidity. In his series of observations of 755 cases of cardiovascular syphilis, Peralta noted that the therapeutic paradox and the Herxheimer reaction were the most frequently encountered immediate untoward reactions but that penicillin in this respect could be better than the previously employed antisyphilitic agents; that the coexistence of congestive heart failure does not seem to be a contraindication for penicillin therapy; on the contrary, cardiac compensation can be helped by the administration of penicillin simultaneously with the usual treatment for cardiac failure. He did, however, feel that aortic aneurysm with large dilatation and acute myocardial infarction are serious contraindications for penicillin therapy. In spite of the usefulness of penicillin, Peralta feels that the prognosis of complicated cardiovascular syphilis seems to remain unchanged with the advent of penicillin treatment.

Changes in the Incidence and Types of Heart Disease: A Quarter-Century Follow-Up in a Southern Clinic and Hospital.—Hutcheson and his co-workers [112] set out to determine the incidence and types of organic heart disease among new hospital and clinic patients treated in a Southern medical center from September, 1951, through February, 1953, and to compare the findings with two studies reported approximately 25 years previously from the University of Texas Medical Branch. The latter reports emphasized the high incidence of syphilitic heart disease and low incidence of rheumatic heart disease in the South. The present study showed that of 34,342 new patients 1,000 had organic heart disease. Of these, 23 (2.3%) had syphilitic heart disease. Thus, syphilitic heart disease showed a marked drop in incidence in spite of the fact that Negroes constitute a substantial proportion of this series. Ranking among the three most frequent etiologic types 25 years ago, syphilis is now rarely seen among new patients and constitutes only 2.3% of the cases. Public education, early diagnosis, and effective treatment have combined to make it a vanishing disease.

Studies in Cardiovascular Syphilis: III. The Natural History of Syphilitic Aortic Insufficiency.—In the third of their remarkable series of studies of cardiovascular syphilis, Webster and his group [113] have delineated the natural history of syphilitic aortic insufficiency in order to create a base line for evaluation of therapeutic results in this condition. This study appeared simultaneously

in the *American Journal of Syphilis, Gonorrhea, and Venereal Diseases* and the *American Heart Journal.*

The paper begins with the statement "Extraordinary as the statement may sound, the enormous world literature on the prognosis and the effect of treatment of cardiovascular syphilis is, with a few exceptions, of little value." The almost total absence of controls in attempting to evaluate prognosis in relation to treatment in a chronic disease such as cardiovascular syphilis is cited as one basis for this statement. It is pointed out that the prognosis in the absence of treatment must be known if one is to judge the efficacy of therapeutic measures. One thousand twenty patients suffering from syphilitic aortic insufficiency and seen in New York Hospital and the Johns Hopkins Hospital during the last 20 years formed the basis of this study. Since previous reports from this group had shown that the material in the two hospitals was not comparable in such variables as age, sex, race, and treatment, a statistical matching process was set up to overcome these disparities. The groups to be compared with respect to their influence on prognosis were matched on a proportional basis with respect to treatment, age, sex, race, work status, and presence of symptoms prior to diagnosis. The matching process was carried out in such a way as to make the proportional distribution in the groups to be compared the same with respect to these six variables. Over three-fourths of the patients were traced for 17½ years or more after the diagnosis was made. "Traced" means that the status of the person, living or dead, was known. The percentage of patients hospitalized increased over the course of years in a linear fashion. Study of survival of patients after diagnosis showed that 50 to 60% were alive after five years; only 13%, after 20 years. The difference in survival between Negro men and white men was less than expected. Twenty per cent of the white males and 12% of the Negro males survived for 15 years. A moderately higher percentage of the patients diagnosed before reaching the age of 40 years survived than did those first diagnosed later in life. At whatever age aortic insufficiency was discovered, the chance of survival was much less than for the standard population. Most of the patients in this series were laborers, who, for economic reasons, were unable to avoid heavy physical exertion until forced to do so by the symptoms of their disease. As might be expected, those who were performing light work or no work at the time of beginning treatment (probably usually because of cardiac symptoms) showed poorer survival than those who were doing heavy work. Development of symptoms of congestive heart failure or angina pectoris was found to have an adverse effect on survival. Those remaining free of symptoms throughout the period of observation survived longest. Next in order were those with no symptoms at diagnosis, those with symptoms at diagnosis, and those with symptoms at diagnosis or later. Of patients who remained free of congestive failure, 67% survived for 10 years following diagnosis, whereas of those who presented congestive failure at the time of diagnosis or later only 3% survived for 10 years. Ten-year survival was 29% for those remaining free of angina pectoris and 17% for those who developed this symptom. Angina, though important, is not as catastrophic a development as congestive failure in these patients. Treatment received prior to the time of diagnosis of cardiovascular syphilis had relatively little effect on survival. About 75% of the patients who died had symptoms of cardiovascular disease at the time of death. Of 219 patients autopsied, diagnosis of syphilitic aortic insufficiency was substantiated in 93% at the New York Hospital and in 84% at the Johns Hopkins Hospital.

Aneurysm of Innominate Artery.—Gay and Walker [114] review the clinical and roentgenological findings in aneurysm of the innominate artery along with their report of 18 cases. These aneurysms, almost invariably due to syphilis, comprise about 3% of all aneurysms. The more commonly encountered clinical features are pain, pulsatile right anterior cervical mass, dyspnea, hoarseness, cough, dysphagia, venous congestion of

face and neck, and pupillary abnormalities. The reader will note that these clinical findings are largely dependent upon the pressure phenomena resulting from expansion of the vascular mass.

Roentgenologically, a right paratracheal superior mediastinal density is present, which exhibits pulsation in about one-half of the cases. Peripheral calcium deposits are common. The trachea and esophagus are displaced to the left and posteriorly. Esophageal displacement to the right excludes the diagnosis of innominate artery aneurysm. Angiocardiographic findings are diagnostic.

In the differential diagnosis of all right superior mediastinal masses, aneurysm of the innominate artery should be considered.

Rupture of Aneurysm into Stomach.—Rupture of a syphilitic aneurysm of the thoracic aorta into the stomach was reported by Renner and Sindelar.[115] Their patient was a 61-year-old Negro who died 17 hours after the onset of symptoms. The essayists consider the following triad as diagnostic of rupture of a thoracic aneurysm into the stomach: (1) the occurrence of severe substernal pain of sudden onset, (2) profuse hematemesis, and (3) a rapidly expanding epigastric tumor, conforming to the gross anatomy of the stomach.

Rupture of Aneurysm into Esophagus.—Perforation of an aortic aneurysm into the gastrointestinal tract is an extremely rare cause of hematemesis and melena. Such a situation was reported by Calenda and Uricchio[116] as it occurred in a 65-year-old white man with syphilitic aortitis and a saccular aneurysm of the descending aortic arch with rupture into the esophagus. Baer[117] notes, in a letter to the editor, that this is not so rare. He and his colleagues have made reports in the past eight years indicative of this.

Dissecting Aneurysm of the Aorta: Report of Six Cases with Etiopathologic and Diagnostic Considerations.—Jackson and Slavin[118] discuss the etiopathology and diagnosis of dissecting aneurysm of the aorta in combination with other disease entities and report six proved cases. One of these, a 74-year-old white man, also had syphilis. Syphilis is not considered an etiologic factor in the causation of dissecting aneurysm. It produces a fusion rather than a dissection. The fact that several cases with positive reactions and with syphilitic aortitis at autopsy have been reported in the literature does not prove that syphilis played an etiologic role but rather that syphilis was present in addition to the dissecting (nonsyphilitic) aneurysm.

Rupture of Aortic Aneurysm into Superior Vena Cava.—A review of the literature from 1883 to the present time disclosed 117 previous cases of an aortic aneurysm which ruptured into the superior vena cava. The usual clinical appearance and findings as obtained from these reports are discussed by England,[119] and an additional case in a 56-year-old white man is reported. The diagnosis in this case was syphilitic aortic aneurysm with arteriovenous fistula connecting the aneurysm with the superior vena cava.

Rupture of an Aortic Aneurysm into the Pulmonary Artery.—Jennings[120] cites the case history of a 44-year-old man in whom a syphilitic aneurysm ruptured into the main pulmonary artery. The case emphasized the fact found in others previously reported that perforation may not be accompanied by precordial pain. It also showed the importance of catastrophic cardiac failure and a positive Wassermann reaction in making full assessment of a case where a mill-wheel murmur is present, for in it neither roentgenography nor electrocardiography gave distinct findings.

Aortic Arch Syndromes.—On the basis of an analysis of over 100 patients with aortic arch syndrome, of whom 35 have not been previously reported, Ross and McKusick[121] present cases in which the seat of the disorder was near the origin of the great vessels from the arch of the aorta. Syphilitic aortitis is considered the commonest cause of the syndrome, while the presence of aneurysm is by no means essential. Saccular aneurysm was found in less than half the patients with great vessel obstruction due to aortic

syphilis. In all syphilitic patients, with and without aneurysm, intimal proliferation and cicatrization represented the most common mechanisms of the obstructions. Secondary atheromatosis of the syphilitic aorta was an important contributing factor in great vessel obstruction.

NEUROSYPHILIS

Neurosyphilis and Trauma.—Vernon and Davis [122] detail a case of neurosyphilis which was precipitated by trauma. The injury to the head of a vigorous healthy middle-aged adult engaged in a heavy occupation brought on several severe symptoms of neurosyphilis. He had bladder paralysis and severe pain in the shoulders shooting down the arm, suggestive of tabes, and his euphoria was considered typical of paresis. The extreme weakness of the hands, suggestive of spinal atrophy involving the anterior motor horn cells, may be classified as "syphilitic polio."

Mental Disease Among Negroes in New York State.—Malzberg [123] contends that Negroes had significantly higher rates of first admissions to hospitals for mental disease than the white population. The greatest divergence was found with respect to general paresis. The average annual rate of first admissions among Negroes was 229.6 per 100,000 Negro population. The rate of general paresis was 33.9. The average annual rate for first admissions of whites was 110.3 per 100,000 white population. The rate of general paresis was only 5.8 among the white population. The difference was even greater with respect to psychosis with other forms of syphilis of the central nervous system, the rates being 1.0 and 10.0 for whites and Negroes, respectively.

Studies in Pallesthesia.—Goldblatt [124] has extended his studies in sensitivity to vibration stimuli to syphilis and lymphogranuloma venereum. He reports that, by means of quantitative determination of perception of vibration, a marked loss of vibratory sense is found in untreated patients with these two venereal diseases. In patients with syphilis, a rapid increase of vibratory sensation beginning 4 hours after the first injection of penicillin and subsiding within 72 hours is considered by the author as suggestive of a Herxheimer reaction. However, metal chemotherapy caused no such effect. Following effective treatment, the vibratory level rises to normal in a few years after treatment. The author considers his test a sensitive indicator of the state of activity of disease and states that progression and relapse are often foreshadowed by a premonitory fall in the level of vibratory appreciation.

Gastric Crisis. — Okinaka and co-workers [125] report a case of spinal syphilis in which the patient suffered from attack of gastric crisis and hypersensibility (girdle pain sensation). The autopsy showed pathologic changes in the spinal cord, meninges, and spinal root fibers, between the 5th and 10th thoracic segments. Nerve fibers in the splanchnic nerve were also partly degenerated. These findings corresponded exactly to the clinical symptoms of motor and sensory disturbances. There was no change in the vagus nerve, and so the cause of the gastric crisis could not be attributed to a lesion of the vagus nerve.

Masked Perforation of a Gastric Ulcer in a Case of Tabes Dorsalis.—A case of masked perforation of a gastric ulcer in a tabetic was presented by Doyle and Campbell,[126] suggesting that in tabes dorsalis visceral pain may be diminished or absent. The difficulties in diagnosis are stressed and the relevant literature is briefly discussed.

Observations of Gastric Motility During Gastric Crisis.—A proved case of syphilis with an abnormality in the peristaltic activity of the stomach during a gastric crisis which disappeared after subsidence of the crisis is presented by Patrick and Reeves.[127] The patient was a 47-year-old Negro with a 15-year history of attacks of abdominal pain occurring two or three times yearly and lasting for three or four days.

Tabetic Spinal Athropathy.—Holland [128] reviews the literature on arthropathy as a complication of tabes and discusses symptoms and roentgenologic features. Case reports are presented for five patients seen in

the last 15 months. In four of these the diagnosis of tabetic arthropathy is highly probable. In the fifth case it is likely, although as yet early changes only are present. The patients include three men and two women, ranging in age from 42 to 67. In four cases the diagnosis of tabes was known at the time of x-ray examination. In one patient the spinal condition was a chance finding, and the presence of tabes was thereafter confirmed.

Syphilitic Parkinsonism. — Neill [129] described a case of the Parkinsonian syndrome apparently due to congenital syphilis. The response to treatment with 10,000,000 units of penicillin was satisfactory. Syphilis is a rare cause of Parkinsonism. However, it should be considered in those cases that develop in the 30 to 50 age group, particularly if there are any anomalous clinical features.

OCULAR SYPHILIS

A number of interesting reports on the various aspects of ocular syphilis have been reported during the past year. A paper, entitled "The Causes of Blindness in England 1948-1950," by Prof. Arnold Sorsby, has been published by the Ministry of Health.[130] It is based on an analysis of more than 19,000 blindness registration certificates. Syphilis accounted for 1.2% of the cases, while ophthalmia neonatorum, diseases of the central nervous system, and trauma accounted for less than 1%. According to Conrad Berens,[131] national and international statistics reveal that approximately 15% of the blind lost their vision because of uveitis caused by various diseases, including syphilis and gonorrhea. Ocular manifestations of syphilis in the uveal tract include granulomatous iritis, which is seen in approximately 5% of the cases in early acquired syphilis and in 8% of cases of secondary syphilis. Diagnosis of gonorrheal uveitis which is of the nongranulomatous type is difficult because there is no typical clinical picture, and etiologic diagnosis must be based on past or present gonorrheal infection. The character, origin, and diagnostic significance of pupillary changes in neurosyphilis are discussed by Jaffe.[132] Pupillometric evidence is offered in support of the view that intracranial involvement occurs early in syphilis.

Reversibility of the Argyll Robertson Pupil in Tabes.—Pines [133] has observed some signs of reversibility of the Argyll Robertson pupil in three patients with tabes, treated by an original preparation of sodium iodide, magnesium thiosulphate, thiamine, and a local anaesthetic, administered intramuscularly.

Unilateral Argyll Robertson Sign.—Thiébaut and Helle [134] give details of a case and describe how the unilateral sign may help to locate the site of the lesion. To produce the miosis, the sympathetic nerves must be involved as well as the parasympathetic; the most likely site is the ciliary ganglion and the sympathetic plexus around the adjoining ophthalmic artery.

Adie's Syndrome and the Adler-Scheie Mecholyl Test.—The literature is reviewed and case reports are presented, by Sprofkin,[135] of three patients with Adie's syndrome, or tonic pupil. One patient had a psychoneurosis; another had amyotrophic lateral sclerosis, while the third had late latent syphilis. The author discusses the diagnostic problem presented by the tonic pupil in differentiating it from the Argyll Robertson pupil of neurosyphilis. When the complete Adie's syndrome is present and the deep reflexes are entirely or partly absent, a greater similarity to tabes dorsalis is presented. The usefulness of the Adler-Scheie mecholyl test in the diagnosis of Adie's syndrome is demonstrated.

Ocular Manifestations of Congenital Syphilis.—According to Gross and Meyer,[136] interstitial keratitis, atrophy of the iris, chorioretinitis, retinal perivasculitis, and optic atrophy comprise the most important ocular manifestations of congenital syphilis. The successive stages of interstitial keratitis are detailed, and it is emphasized that, in almost all cases, residua which may be detected by slit lamp examination remain for many years after the acute process has subsided. The

authors conclude that in the absence of other physical signs of congenital syphilis ocular examinations may reveal findings diagnostic of this condition.

Corneal Thickness in Interstitial Keratitis.—The thickness of the normal and diseased cornea (both specific and nonspecific keratitis) was measured in a series of 10 patients by Cook and Langham.[137] These investigators observed changes in corneal swelling, opacity, and vascularization after the topical and subconjunctival administration of cortisone. They found that a marked swelling of the cornea precedes vascularization and that cortisone inhibits the extension of the corneal swelling and vascularization.

Cogan's Syndrome.—The 17th case of Cogan's syndrome, the first in a child, was reported in detail by Stevens.[138] The entity consists of a triad of bilateral interstitial keratitis; involvement of both components of the eighth nerve, with progressive bilateral deafness, and consistently negative serological and clinical evidence of syphilis. Leucocytosis and eosinophilia may be associated. The cause is unknown, but one must exert care not to confuse this syndrome with congenital syphilis.

SYPHILIS IN PREGNANCY AND CONGENITAL SYPHILIS

A number of rare manifestations of congenital syphilis have been reported during this review period. Additional data on congenital syphilis have been given in the section on ocular syphilis. The *British Journal of Venereal Diseases*[139] has in editorial comment made a comprehensive statement of the prevention of congenital syphilis.

Prenatal Serologic Tests.—Because of the new wave of syphilis connected with the occupation of Norway by the Germans from 1940 to 1945, the Norwegian Public Health Service in January, 1948, requested that serologic tests for syphilis be performed on all pregnant women.[140] Throughout the five-year period (1948 to 1953) under review, 1,371 of the women tested gave positive reactions, a mean rate of 0.78% for the whole period. The highest syphilis rate was 1.23%, in the first year. During the remaining four years, there was no statistically significant fall in the syphilis rate, which in the last year was 0.78%.

Syphilis in Pregnancy.—During eight years, 1944-1952, routine serologic blood examinations of 37,540 pregnant women, made by Berlin and Meyrovitz,[141] revealed 153 positive or doubtful reactions. Specific treatment was administered to 111 expectant mothers in 127 pregnancies: 26 women had early symptomatic or latent syphilis (of less than four years' duration); 57 had late symptomatic or latent syphilis; 8 had congenital syphilis; in 11 the stage could not be ascertained; in 9 there was only questionable evidence of syphilis. In 25 cases the patients received arsphenamine and bismuth therapy; in 12, metal chemotherapy concurrently with penicillin, and in 80, penicillin alone. Aqueous penicillin every three hours, totalling 4,000,000 to 8,000,000 units, was given to 56 patients in hospital, and pencillin procaine, 600,000 units daily for 10 days, was given to 52 out-patients. In most cases syphilotherapy was started in the second half of the pregnancy. There were eight treatment failures, four possibly and four probably due to syphilis. They all occurred in patients with early syphilis, after treatment with metal chemotherapy (four), penicillin (three), and chemotherapy with penicillin (one). In addition to the important advantages of convenience of application, almost complete lack of toxicity, and brevity of treatment, penicillin given to an expectant mother has superior therapeutic effects and offers greater safety for the child, according to these authors.

Familial Investigation in Syphilis.—While numerous publications, especially in the United States, have dealt with the results of contact investigation in acquired contagious syphilis, little has been written about the familial contacts of patients suffering from congenital, latent, or late acquired syphilis. Six hundred seventy patients, comprising 542 with acquired noncontagious syphilis and 128 with inherited disease, were asked by

Macfarlane [142] to cooperate in having their family contacts examined. Of 2,284 contacts named, 218 had died, death being due to syphilis in at least 4 instances, and 491 were not examined for various reasons; 1,575 were tested, mainly in the venereal disease department. Three hundred twenty-eight contacts (21%) were found to be infected, the respective incidence in contacts of the acquired noncontagious and congenital type of syphilis being 13% (164) and 48% (164). Syphilis was detected in 88% of mothers, approximately 50% of fathers, and 25% of brothers and sisters of the congenitally infected; 24% of spouses of those with acquired (noncontagious) syphilis were likewise infected. Two hundred forty-seven contacts had serological examinations only, and this may well have been a weakness in the author's scheme, since some could have been serologically negative and yet have presented clinical manifestations of the disease, especially of the congenital type. The prospects of family contacts reporting for examination were not necessarily improved by (*a*) the attendance of both parents for examination or the possibility of both being infected; (*b*) the obvious pain or discomfort suffered by the original patient who had acquired syphilis, since the response of contacts of patients with latent syphilis equaled that of contacts of those showing gross cardiovascular syphilitic disease; (*c*) the presence in a large family of a congenitally-infected young patient with either severe stigmata or obvious suffering from the effects of the disease, and (*d*) the age of the original patient, children eliciting no better response amongst their contacts than adults. The prospects of contact cooperation were considerably improved when (*a*) the original patient showed little or no default during treatment or surveillance; (*b*) when less than 12 months had elapsed between the patient's initial attendance and the first request for contact examination; (*c*) when the contact was female. The great majority of patients should be told the nature of their disease; otherwise the discovery of the truth from a second-hand source may undermine their confidence in the venereal disease department, with consequent default. Even when armed with this knowledge, the patient's dread of being "discovered" through contact investigation may cause him to leave his family contacts out of the picture, hoping they are uninfected, rather than run the apparently more obvious risk of grave domestic upheaval. Therefore, to be successful, a contact investigation scheme should be so designed as to remove the patient's fear. The following provisions are desirable: (*a*) suitable premises, not in a venereal disease department; (*b*) carefully-chosen medicosocial personnel; (*c*) wholehearted cooperation of family doctors, either in examining contacts or in persuading them to attend for testing. In cases in which the disease is latent it is all the more difficult for the infected to realize the need for their cooperation. (Latent syphilis was noted in 45% of the original patients and 72% of contacts.) Once the patient's fear was circumvented by an essentially practical contact-tracing scheme, the procedure attempted proved to be well worth while and likely to eliminate the undetected, infected contacts who would appear in later years with advanced manifestations of the disease.

Congenital Syphilis Among Living Infants in Nagasaki.—In conjunction with genetic studies carried out by the Atomic Bomb Casualty Commission in Nagasaki, Japan, Wright and Wright [143] studied the incidence of congenital syphilis among living infants in this community. On the basis of maternal and infant serologic tests, history, physical examination, and roentgenograms of the long bones, 7.4 per 1,000 live infants were diagnosed as syphilitic. The incidence of congenital syphilis is highest among those born to younger mothers, particularly those in the 15- to 19-year-old group. A gradual decline in the rate of transmission was noticed with increasing maternal age.

Congenital Syphilis of the Stomach.—Mitchell [144] reported a case of congenital syphilis of the stomach with 14-year follow-up. Treatment with iodides, bismuth, and arsenic caused disappearance of symptoms,

return to normal roentgenologic appearance of the stomach, and disappearance of achlorhydria. Of the three cases of congenital syphilis of the stomach now in the literature, one operated upon (gastric reaction) died and two given antisyphilitic therapy recovered.

Congenital Syphilis of the Lungs.—Edmondson [145] reported in detail congenital syphilis of the lungs of a stillborn female infant. The gross lesions were exclusively in the lungs, which were atelectatic, and scattered throughout their substance were numerous globular tumors varying from 2 mm. to 1 cm. in diameter. These tumors were yellowish white and, on section, were rubbery and uniform in consistency. A number of the more superficial tumors caused bulging of the lung surface and were quite sharply defined. On microscopic study, a chronic interstitial pneumonia was present. The classic diffuse pneumonia alba was absent. In the nodules of solid tissue, the bronchi showed up well, and in some places alveoli were lined with cubical epithelium. Sections stained by Levaditi's method finally established the diagnosis by revealing a considerable number of spirochetes in both tumor and nontumor areas. Although spirochetes were found microscopically in the liver, the reaction to them appeared to be minimal in this organ.

Congenital Aneurysm.—Bowie and Simpson [146] described the case of a man, aged 38 years, with signs of aortic incompetence and of thoracic aortic aneurysm. They attribute the aortic valve lesion to rheumatic heart disease, the aneurysm to congenital syphilis.

Both of these statements are debatable. The presumption of a rheumatic origin of the aortic valve defect is based on the history of two attacks of rheumatic fever in youth and the development of ausculatory evidence of aortic regurgitation two months after the initial episode. The cause of the aortic aneurysm demands more detailed consideration. The diagnosis of congenital syphilis was made on the grounds of a repeatedly reactive blood serum in a youth of 19 with no evidence of acquired disease and with stigmata suggestive of congenital infection. There were no unequivocal signs of congenital syphilis, but the incisor teeth were rather small and deformed and there were circumoral rhagades. The roentgenogram of the chest showed linear calcification in the walls of the aneurysm, a condition many consider diagnostic of syphilis. On this sign Bowie and Simpson laid great stress.

Paroxysmal Cold Hemoglobinuria in Treated Congenital Syphilis.—Rosenblum and Cetnar [147] present the case of a 22-year-old male Hawaiian with paroxysmal cold hemoglobinuria, who had been successfully treated for congenital syphilis with heavy metals and penicillin. The patient was born and had always lived in the subtropical climate of Hawaii. The manifestations of hemoglobinuria did not occur in any degree of severity until he became exposed to the cold climate of Korea.

Third-Generation Syphilis.—Caver [148] presents in detail what might be considered a case of third-generation syphilis transmitted directly through the congenitally syphilitic mother. He points out how this misdiagnosis will be made when the material is viewed superficially and that more intensive study of his case showed early syphilis in both parents. This suggests that the wife was reinfected extramaritally or premaritally, with subsequent transmission to the husband, or, equally likely, that the husband was in relapse from his original infection and infected his wife, according to Schoch's principle of "ping pong" syphilis. Bonugli [149] also made a detailed description of two cases of third-generation syphilis occurring in the same family. The coincidental findings of interstitial keratitis in all the surviving members of two generations of this family is also noted. Finally, the typical slow insidious evolution of syphilitic manifestations extending over a quarter of a century in a hitherto "unmanaged" family group is described.

GENERAL THERAPY

The status of therapy for all phases of syphilis has become largely consolidated. However, certain problems such as the ulti-

mate results of treatment and the possibility of still further shortening of courses are still unsolved. This review period sees more efforts in these directions plus further information on a variety of aspects of the syphilis treatment problem. Danbolt [150] outlines the development of syphilis therapy since 1943 and points to the importance of the introduction of repository penicillin G procaine in oil with 2% aluminum monostearate (PAM) preparations as well as new penicillin G salts. The clinical and laboratory basis for the action of penicillin in treponematoses is also reviewed and reference made to the work of WHO and the marked achievements in mass penicillin programs in underdeveloped areas. Information is also given on the natural course of untreated syphilis as studied by Bruusgaard in 1929 in material available at the University Clinic of Oslo between 1821 and 1910. This material covers some 2,000 untreated syphilitic patients, on which a further follow-up study is currently being carried out by Dr. Gjestland, of the University of Bergen, with assistance from the Division of Research, Grants, and Fellowships of the U. S. Public Health Service. It has been possible from 1947-1953 to obtain adequate information on 75% of the dead or living patients in this series, and the preliminary results show that the complications in untreated syphilis approximate 35% of the infections; 15% of these manifestations have been benign tertiary syphilis, 10%, cardiovascular syphilis, and 9%, secondary syphilis. A detailed account of this material will shortly be published in the WHO Bulletin (or Monograph Series). According to Thomas,[151] the understanding of syphilis has not kept pace with the advances in treatment, and for that reason numerous problems plague the physicians in the diagnosis of the disease. Syphilis actually occurs as two major diseases—the acute and chronic stages, which differ clinically and immunologically. The acute stage ends with the final disappearance of early lesions, but immunologically it ends only when the body tissues have developed a more or less permanently altered reactivity to the treponeme. Syphilis is one of the most complicated diseases known to medicine. The decision as to whether or not to treat syphilis requires greater diagnostic acumen than merely treating patients with positive blood tests. Prolonged seropositivity after treatment of early syphilis, in the absence of relapse, reinfection, or positive spinal fluid findings, does not mean a continuance of the infection. Increasing the amount and duration of treatment has no effect in shortening the duration of seropositivity after treatment. The fact that in many instances there is no direct way of proving permanent arrest of the disease has been the cause of much confusion in evaluating the effect of treatment, especially of late syphilis.

Penicillin Treatment of Treponemal Disease.—Idsøe and Guthe [152] present concepts of syphilis and current practices in penicillin therapy based on repository preparations of the PAM type and point out that a survey of national and international trends indicates not only that PAM has become the drug of choice in the treatment of all stages of the infection but also that most venerologists employ it without additional metal chemotherapy. The laboratory and clinical basis for penicillin treatment of syphilis (including time-dose relationship), the selection of PAM preparations meeting international requirements concerning the duration of effective penicillinemia, and the various modes of penicillin administration, as well as the significance of the duration of the infection and the immunological processes, are being discussed. The authors also consider the principles of medical control examinations and of follow-up of syphilitics treated with repository penicillin; the present status of penicillin therapy, including acceptable dosage schedules, in early, latent, and late syphilis; the preventive treatment of pregnant syphilitic women; the special problems relating to prophylactic parenteral or peroral use of penicillin before exposure, and preventive (abortive) treatment of syphilis in the incubation period.

TREATMENT OF EARLY SYPHILIS

Treatment Before Diagnosis in Venereology.—Willcox [153] has presented a good case for the concept that abortive treatment for the venereal diseases is unsound, perhaps ineffective, and often harmful. This departure from fundamental principles should be discouraged. King [153a] is also against treatment before diagnosis.

Current Treatment Practices in Early Syphilis.—In order to appraise recent trends in syphilotherapy in the world, WHO carried out a detailed study of treatment practices in early syphilis. According to Willcox,[154] 277 replies were received from 55 countries giving particulars of 294 schedules (representing 68.6% of the questionnaires sent out in the survey). A total of 65.3% of the participants used penicillin alone, and 28.9% used it in combination with other drugs. In North America all clinics relied solely on penicillin, as compared with 52.2% in Europe. The commonest dosage of penicillin in all stages of early syphilis was 4,800,000 to 6,000,000 units, but appreciably larger doses were used in Europe than in the Americas, South-East Asia, and the Western Pacific regions. In Europe there were single instances of 36,000,000 units being given. "Consolidation" treatment was given in none of the North American clinics, seldom in Asia, by about one-third of the participants in Central and South America, and, for secondary syphilis, in 59% of the European schedules. It is suggested that these findings, 10 years after the introduction of penicillin in syphilotherapy, are of general interest to venereologists and health workers, since they indicate a situation which is not dissimilar to that immediately after the first World War, when the new arsphenamines had been introduced.

Treatment of Early Infectious Syphilis with Benzathine Penicillin G.—Smith and his co-workers [155] treated 127 patients with dark-field-positive primary or secondary syphilis with a single injection of 2,500,000 units of benzathine penicillin G (N,N'-dibenzylethylenediamine dipenicillin G; Bicillin). In their hands, this preparation in this dosage gave a mean blood level of 0.134 units per cubic centimeter for the first week, 0.058 for the second week, and 0.097 for the two-week period. Dark-field examinations became negative within a 15-hour period following treatment. Eighty-six of the patients have been observed for more than six months, and 50, for more than one year. At the end of six months, 81% of the seropositive primary patients and 65% of the secondary patients had become seronegative. Of the four patients requiring retreatment, three had definite epidemiological and clinical evidence of reinfection. Treatment of eight women before or during pregnancy was successful in all cases in preventing infection of the infant. Comparison of the post-treatment serologic pattern of these patients with that of a group of patients previously successfully treated with penicillin procaine in oil with 2% aluminum monostearate (PAM) showed no essential difference. Serologic results 12 to 15 months following treatment showed that the benzathine-penicillin-G-treated patients compared very favorably with the group previously treated with PAM. Two anaphylactoid reactions occurred, and four patients developed dermatitis medicamentosa. The incidence of significant reactions was approximately 1%, and the duration of reaction was brief, despite the long persistence of a significant blood level. The authors conclude that a single injection of 2,500,000 units of benzathine penicillin G for early infectious syphilis produces results equal, if not superior, to those obtained with presently accepted treatment schedules. A second report on the efficacy of benzathine penicillin G in the treatment of early infectious syphilis has been presented by Shafer and Smith.[156] This drug avoids the use of oil and aluminum compounds and maintains treponemicidal blood levels over a much longer period than PAM with the same dose. The report includes 196 patients with early infectious syphilis who were given a single injection of 2,500,000 units. The seronegativity rates after three months were 65% for seropositive primary syphilis and 25% for secondary

syphilis; at six months the rates were 80% and 60%, respectively. At the end of the observation period, satisfactory results were recorded in 96.6 to 100% of the primary syphilis patients and in 92 to 95% of those treated for secondary syphilis. The respective cumulative retreatment rates were 3.4 and 4.1%. The incidence of reaction of significance is reported to be less than 0.3%.

The results of the secondary syphilis treatment with benzathine penicillin G were then compared with those obtained with single-injection schedules of 2,400,000 and 4,800,000 units of PAM. The cumulative retreatment rates 21 months after treatment were as follows: benzathine penicillin G, 4.1%; PAM (2,400,000 units), 14.2%, and PAM (4,800,000 units), 5.1%. Guthe and Danbolt [157] also describe preliminary results with benzathine penicillin G and N'benzylphenylethylamine penicillin salts with repository effect in the treatment of syphilis. The results show that a few intramuscular injections, or even one, of relatively small doses of these salts in aqueous solution can maintain effective penicillinemia for several weeks and that the side-effects do not appear to be more frequent than those occurring when penicillin procaine preparations of the PAM type are used. Since the basis for effective penicillin treatment of syphilis and other treponematoses is the maintenance in the blood and tissues of adequate penicillin concentrations of long duration (0.03 units per milliliter or more), the new benzylamine penicillin salts present possibilities for the further simplication of syphilotherapy, and extensive clinical trials are now being undertaken, under WHO auspices, in several countries. Should the preliminary favorable results (which include four cases of early syphilis treated at the Clinic for Dermatology, University of Oslo) be confirmed, the simplified schedules might have considerable importance for patients in itinerant occupations, e. g., seafarers, and for mass treatment programs against treponemal diseases in underdeveloped areas. At present, peroral medication with benzylamine penicillin preparations is not recommended for prophylactic or curative purposes in either syphilis or gonorrhea.

Experimental Rapid Treatment of Early Syphilis with Penicillin.—A detailed study was carried out by de Graciansky and Grupper [158] and their colleagues of 53 patients treated with penicillin in the early stages of syphilis. There were three groups of patients: 10 in the preserologic stage of primary syphilis, 15 in the serologic stage of primary syphilis, and 28 in the early stage of secondary syphilis. Each patient received three intramuscular injections seven days apart; the first was of 3,000,000 units, and the others of 1,500,000 or 3,000,000 units each, depending on the patient. The following results were noted: 1. Clinical symptoms definitely disappeared in all patients. 2. Treponema disappeared from the lesions within 24 hours after the first injection. 3. Tests of the serum were not positive after treatment in patients whose serum reactions had been negative before treatment; their cerebrospinal fluid also remained normal. Negative response or decrease in rate of reaction was obtained in patients whose serum gave a positive reaction before treatment. 4. Quantitative amelioration in the serum appears considerably sooner than qualitative amelioration and thus constitutes a better sign to be watched during treatment. 5. Before treatment, results of Nelson's test were positive only in the patients with a high rate of reaction; after treatment, negative responses were obtained in patients who had been treated early in the disease but results of the Nelson reaction of patients treated late in the disease were not influenced. 6. None of the persons who had sexual relations with the patients showed any signs of syphilis nor did the children born of these patients. 7. The side-effects of therapy were insignificant. No precautions were sufficient to prevent the appearance of a Herxheimer reaction in 50% of the patients, but preventive therapy with cortisone (100 mg. of cortisone daily for five days) reduced this to an inconsequential level. The reaction may appear after any of the three injections. 8. Although the amount of penicillin in the blood varied unpredictably

in each patient, these differences did not influence the results of therapy in any way. 9. The authors are of the opinion that their therapy was actually more extensive than is necessary for early syphilis; they plan to experiment with the use of one injection only. A report on this is forthcoming.

Feldreich,[159] in an experience of 36 cases of early syphilis treated with 10,200,000 units administered within 17 days in daily doses of 600,000 units, obtained cure rates for primary syphilis of 57% after two months and 96% after four months. For secondary syphilis with clinical symptoms the corresponding figures were 14 and 57%, respectively.

Treatment of Treponemal Diseases with Penicillin Salts.—Single or multiple intramuscular injections of Panbiotic, a new combination of three penicillin salts, were given for assay studies to 94 hospital patients by Rein and his co-workers.[160] A single dose of 2 ml. of aqueous suspension provides 300,000 units of penicillin G potassium, 300,000 units of penicillin G procaine, and 600,000 units of benzathine penicillin G. Microbiological assay determinations indicated that higher and more prolonged blood levels are obtained with a single injection of 2 ml. of Panbiotic than with a single injection of 4 ml. of microcrystalline penicillin G jelled in oil with 2% aluminum monostearate, even though both contain 1,200,000 units of penicillin. Urticaria or other untoward reactions did not occur in any of the 94 patients. Preliminary clinical studies in the therapy of syphilis, yaws, and pinta with this new triple penicillin preparation are highly encouraging. Since an adequate amount of therapy can be administered in a single injection without fear of any increased evidence of serious untoward reactions, this type of penicillin preparation should be of special value in those countries in which the majority of patients with treponemal diseases must be treated with single injection schedules on an ambulatory basis in rural areas.

Treatment of Early Syphilis with a Single Injection of Penicillin G Procaine in Oil and Aluminum Monostearate.—Thomas and his co-workers[161] report additional findings on 174 patients with primary or secondary syphilis who were treated with a single injection of 1,200,000, 2,400,000, or 4,800,000 units of penicillin procaine in oil with 2% aluminum monostearate. All patients had been followed clinically and serologically for periods ranging from 9 months to 5 years. All of 50 patients with seronegative or seropositive primary syphilis, followed for 9 to 60 months, were seronegative at the time of last examination. However, only 73% of 124 patients with secondary syphilis, followed for the same time interval, were seronegative. Serologic improvement occurred in 12.9%, and 13.7% were retreated because of seroresistance, relapse, or reinfection. The authors conclude that a single injection of 1,200,000 units of this type of penicillin is a satisfactory procedure for primary syphilis. They do not recommend single injection treatment for secondary syphilis, but, if it is used, they advise a dosage of 2,400,000 units.

Long-Term Studies of Results of Penicillin Therapy in Early Syphilis.—A further report describing the results of therapy in the Blue Star Study of the U. S. Public Health Service has been presented by Shafer, Usilton, and Price.[162] Of the 1,570 patients selected for inclusion, 1,336 (85.1%) are still under observation, and 89.4% of the scheduled observations have been completed. One objective of the study was to test the hyphothesis that patients relapsing from follow-up have the same experience as those remaining under observation, and evidence is presented which indicates that this is the case. The major objective of the program, however, was to study the antisyphilitic properties of penicillin, and data are presented showing the results obtained with penicillin alone and in conjunction with oxophenarsine hydrochloride (arsenoxide) and bismuth at the sixth post-treatment year. Satisfactory results were recorded for 98 to 99% of the patients with primary and secondary syphilis (including those retreated). Seronegativity rates were 81% for patients given combined penicillin-arsenic-bismuth therapy and 80.7% for those treated with penicillin alone, while retreatment rates were 17.4 and 16.3%, respectively.

When cases treated with "adequate" dosages of arsenic and bismuth are analyzed by the same statistical method as that employed in evaluating penicillin, the superiority of penicillin is clearly evident. Reference is also made to the dangers to the patient inherent in treatment; with penicillin alone the rate of reaction was 3.1 per 1,000 in the group of 186,677 patients who were treated during July, 1946, to July, 1950, while the rate of reaction in combined penicillin-arsenoxide therapy was 12.5 per 1,000 in the 156,294 cases treated during the same period. Danbolt and Berdal [163] found the results of a follow-up examination of 192 patients suffering from early syphilis, treated with penicillin-arsenoxide-bismuth, to be very satisfactory. It is still too early to determine whether eventually this combination therapy will be more effective than penicillin alone in the treatment of early syphilis. Thomas and Gleesen [164] present a nine-year follow-up on a significant number of patients treated for primary or secondary syphilis with multiple injections of oxophenarsine hydrochloride, U. S. P. (Mapharsen) and typhoid vaccine. Nine years after treatment, 68% of the patients were seronegative, 14.5% had been retreated for reinfection, and 14.8% had been retreated for treatment failure. In no case was progression of the syphilitic infection noted during this observation period. The authors compared these findings with those in a group treated in U. S. Public Health Service treatment centers with penicillin and observed for a five-year period. They found no significant difference in treatment results in these two groups and concluded that short-term arsenical treatment combined with typhoid vaccine is an effective, although outmoded, method of treatment for early syphilis. Perdrup and his colleagues [165] reported on 157 cases of mucocutaneous syphilis treated with penicillin procaine which have been followed for one to four years. Two of the cases relapsed (1.3%). There were six cases of verified reinfection. No definite neurosyphilis was disclosed. Lee [166] presents the following suggestions for handling patients with previously treated syphilis: 1. A patient whose history of initial treatment indicates probable inadequacy should receive a course of therapy in accordance with the diagnosis. 2. A patient who gives a history or has physical signs suggestive of progession of disease since last examination should be retreated. 3. A patient whose serologic titer has increased fourfold or more should be retreated. It is difficult if not impossible in the average case to determine if this represents reinfection or merely serorelapse. 4. A patient whose serologic titer was previously 1:32 Kahn (1:8 VDRL) or greater and has failed to revert below this level deserves a single course of retreatment. 5. A patient whose spinal fluid shows evidence of activity (a cell count greater than five or a total protein value significantly higher than your laboratory's accepted normal value) should be retreated. 6. Any patient with cardiovascular syphilis or symptomatic neurosyphilis who has never received penicillin therapy probably would benefit from such therapy. 7. Regardless of the stage of syphilis, if the patient is a woman all her children and her husband should have serologic tests for syphilis. If the patient is a man, his wife should have such a test.

TREATMENT OF LATE LATENT SYPHILIS

The Epstein group [167] were courageous when they undertook a study of the effects of therapy on late latent syphilis. Their series covered 2,470 patients treated for late latent syphilis with metal chemotherapy and 231 treated with penicillin. They determined the effectiveness of treatment by the incidence of clinical progression per century of patient observation. When arsenic or bismuth or both were used, the incidence of progression was less among patients who had received more than 55 doses than among patients who had received fewer doses, but this was true only when previous therapy had been insignificant. Penicillin did not completely prevent progression, but the data were too meager to allow satisfactory comparison with metal therapy. It appears, however, from these data that a higher incidence of persistently positive Wassermann reactions followed peni-

cillin therapy than metal therapy. Progressions were also more frequent among Wassermann-fast cases than in those that were not Wassermann-fast.

Serologic Observations Following Penicillin Treatment for Latent Syphilis.—Chester, Cutler, and Price,[168] in a report on the serologic response of latent syphilis following penicillin therapy, present an analysis of 447 cases followed for seven years after treatment. A battery of five serologic tests (Mazzini, Kahn, Eagle, Hinton, and Kilmer) was used throughout the study. The Kahn test, being the least sensitive, reverted to negative most rapidly, and the Mazzini test, the most sensitive, reverted most slowly. After seven years, 34 to 53% of patients with a diagnosis of early latent syphilis were seronegative with the various tests. Only 10 to 31% of those with late latent syphilis were seronegative at the same period after treatment. No significant difference in percentage of those seronegative was noted between those who received more and those who received less than 3,400,000 units of penicillin. Patients with early latent syphilis had higher pretreatment titers and had a more rapid drop in titer than did patients with late latent syphilis. In a well-controlled study of serologic response following retreatment, because of seroresistance, of patients with early latent syphilis, Cannefax and Johnwick[169] compared 63 retreated patients with 72 controls who were not retreated, by observation of post-treatment serologic titers. Retreatment did not hasten the reduction of reagin titer, and the authors conclude that seroresistance following treatment for early latent syphilis is not, by itself, an indication for retreatment. Since the retreatment dose was more than twice the amount given initially, the authors feel that the failure of retreatment to cause accelerated fall in reagin indicates that seroresistance is not due to persistance of treponemas in the body. They feel that seroresistance is analogous to the persistence of other immunologic activity after termination of an infection or after active immunization.

TREATMENT OF CARDIOVASCULAR SYPHILIS

Penicillin Treatment of Cardiovascular Syphilis: Uncomplicated Aortitis.—Eisenberg and Brandfonbrener[170] report on the results of penicillin treatment in 43 patients with uncomplicated syphilitic aortitis. In patients with an unquestioned diagnosis of syphilis, diagnosis of aortitis was made on the basis of two of the three following findings: (1) accentuation of the second aortic sound in the absence of hypertension, (2) a systolic murmur over the aorta in the absence of hypertension, (3) presence of a widened ascending or descending aorta on fluoroscopy or x-ray examination.

All the patients remained asymptomatic, and no Herxheimer reactions were noted. In the follow-up period of six months to over two years, no progression in the murmur or in the size of the heart or aorta was noted. The authors conclude that penicillin treatment is safe but that longer follow-up will be needed to determine its efficacy. In a further study of 163 patients with syphilitic aortic insufficiency and/or saccular aneurysm, Eisenberg and Brandfonbrener[171] concluded that penicillin is a safe method of treatment in complicated aortitis. They analyzed the post-treatment clinical course of their patients but stated that no conclusions can be drawn as to the efficacy of penicillin treatment in advanced cardiovascular syphilis without the use of a concurrent control group, which was not available to them.

Effect of Penicillin Treatment on the Microscopic Appearance of Syphilitic Aortitis.—Sinclaire and Webster[172] studied the histologic appearance of the aortas of 10 patients with syphilitic aortitis, aneurysm, or aortic insufficiency who came to autopsy following penicillin therapy. In three patients who had received penicillin two months or less before death a severe degree of lymphocytic and plasma cell infiltration was seen. However, seven remaining patients, all of whom had received penicillin more than 10 weeks prior to death, showed little or no microscopic evidence of syphilitic inflammation in their aortas. The authors conclude

that adequate penicillin therapy modifies the inflammatory process of syphilitic aortitis.

Treatment of Cardioaortic Syphilis with Penicillin.—Despite several accidents reported in the first experiments, Texier and Régnier [173] conclude that it is clear from present American and French work that penicillin is one of the best treatments for aortic syphilis. This treatment does involve some risk, however, and certain precautions must be taken. The authors describe the method they used recently in Bordeaux, France. 1. The patients are kept at complete bed rest and fed a low-chlorine diet after cardiorenal and serologic examination (cardiolipin antigen). 2. They receive 9,000,000 to 20,000,000 units of penicillin G procaine in oil with 2% aluminum monostearate (Flo-Cillin) in daily doses of 600,000 Oxford units in one injection. 3. In order to prevent anaphylactic shock caused by the massive bacteriolysis that occurs with the first few injections and is manifested by general and local (aortic) reactions (Herxheimer reaction), the patients receive concurrently 1 tablet of synthetic antihistamine every four hours, 1 gm. of ascorbic acid per day, and a medicament that has a vitamin-P-like effect. 4. The patients are subsequently kept under clinical and serologic surveillance.

Treatment of Saccular Aneurysms of the Thoracic Aorta.—Johnston and his colleagues [174] have reviewed the surgical procedures employed in the therapy of aortic aneurysm. These include intrasaccular clotting, external reenforcement and removal of the aneurysm followed by suture of the defect, or replacement by a graft.

Treatment of Aneurysms of the Great Vessels by Wiring.—After discussing the etiology and diagnosis of aneurysms of the great vessels, Penick [175] considers indications for wiring the aneurysms, technique used, complications, and results. Well-defined aneurysms in the upper aorta are usually due to syphilis, whereas those in the aorta below the renal vessels are most often of arteriosclerotic origin. However, syphilis may be the cause of those occurring in the great vessels at the base of the neck or in the pelvis and legs. Wiring is applicable to well-defined syphilitic or arteriosclerotic aneurysms of the larger arteries. It is best suited to the saccular aneurysm but may be used in the fusiform type also. Pain is a prominent symptom of syphilitic aneurysms. In these patients the relief of pain following wiring is usually dramatic. A brief illustrative case report is presented of a 36-year-old Negro who was incapacitated by a syphilitic aneurysm of the aortic arch and in whom wiring produced great relief. When symptoms recurred, another wiring was done. This had only a slight beneficial effect, and soon thereafter the aneurysm ruptured. The author believes that wiring of aneurysms of the great vessels offers a great deal to those patients in whom more definitive procedures cannot be carried out. Its simplicity and safety recommend it, and the palliative effects are rewarding.

Excisional Therapy of Aortic Aneurysms.—The application of excisional therapy is dependent upon several factors, the most important of which is the location and the nature of the lesion. Sacciform aneurysms in which the neck is relatively small and the wall of the parent vessel is suitable for suture may be excised with lateral arteriorrhaphy to repair the aortic defect. Lesions of this type are most likely to be of syphilitic origin and are most frequently encountered in the upper thoracic aorta. In 10 consecutive patients with aneurysms in which the procedure of excision and replacement with aortic homograft was done by De Bakey and Cooley,[176] all had an uncomplicated postoperative course except one, who died. All of the patients were over 60 years of age, except 2 in whom the aneurysm was of syphilitic origin. Cooley and De Bakey, in a later study,[177] show that the methods of surgical treatment of aneurysms have been directed chiefly toward obliteration of the aneurysm by promotion of thrombosis within the sac by ligation, introduction of foreign material, or stimulation of periarterial fibrosis. None of these methods has proved satisfactory, and only rarely has any of them achieved a cure. Recent observations on pa-

tients with aneurysm of the abdominal aorta previously treated by Cellophane wrapping and subsequently resected provide good reason to believe that this method not only has limited value but may even be harmful. Excision of the aneurysms, with restoration of continuity, is considered the procedure of choice and may be applied much more frequently than has been previously realized. This can be accomplished in sacciform aneurysms of the thoracic aorta, usually syphilitic in origin, by tangential excision with lateral aortorrhaphy. For aneurysms of the lower thoracic and, particularly, the abdominal aorta, most of which are fusiform and arteriosclerotic in origin, excision of the aneurysm usually necessitates resection of a varying segment of the aorta. Under such circumstances restoration of aortic continuity requires the use of aortic homografts. The technical aspects of the excisional therapy are discussed on the basis of cases. The authors performed resection of the aneurysm and involved aorta with replacement by aortic homografts in 13 cases, in 1 of which the aneurysm was located in the lower thoracic aorta. In all of the 12 cases in which the aneurysm occurred in the abdominal aorta it was fusiform in type, and in 9 of these the aneurysm involved the bifurcation, necessitating its resection. The only death in this series occurred on the 13th postoperative day, of progressive uremia and secondary hemorrhage in a 74-year-old woman. In an addendum the authors say that since the presentation of this report in May, 1953, excision of aneurysms of the aorta with restoration of vascular continuity by aortic homograft has been performed in 14 additional patients. In 11 of these the aneurysm involved the abdominal aorta and necessitated removal of the bifurcation. Three deaths occurred in this latter group, two as a result of coronary thrombosis and the third presumably from pelvic thrombosis. All other patients surviving the operation, including those in the original report, remain well. Bahnson [178] feels that almost all aortic aneurysms are caused by either arteriosclerosis or syphilis. Those due to syphilis are usually saccular, occur predominantly in the thoracic aorta and almost never below the renal arteries, and appear earlier in life and are often associated with erosion of adjacent bone and considerable pain. The prognosis is poor. Syphilitic aneurysms are usually localized ruptures, with a relatively narrow communication between the aneurysmal sac and aortic lumen. Following excision and specific therapy for syphilis, the remaining aorta may be functionally adequate. The first principle underlying treatment of aortic aneurysms is to reduce the diameter of the vessel and the tension on its walls. Any thin, unstable, and weak areas should be removed or adequately reinforced. Whenever possible, the tumor should be removed. Case histories are given for 3 of 12 patients in whom excision was successfully carried out.

TREATMENT OF NEUROSYPHILIS

Prognosis in General Paresis.—It it noted in a foreign letter in *The Journal of the American Medical Association* [179] that in a follow-up study of 457 patients with general paresis and 79 with taboparesis admitted to Horton Hospital between 1942 and 1946, M. Whelen and M. H. Bree (*Lancet* **1**:70, 1954) record that, of those with general paresis, 141 had died, 99 were still in hospital, and 217 had been discharged. The corresponding figures for taboparesis were 30, 12, and 37. For those discharged from the hospital during this period, it was possible to follow 113 with general paresis and 19 with taboparesis for at least five years. Their ages varied from 17 to 67, most of them being in the decade 41 to 50. Most of them had been treated by malaria, but some had been treated with malaria plus penicillin or penicillin alone. Thirty-nine had made a complete recovery; 81 exhibited various degrees of recovery, 11 in stationary states, and 1 could not be classified. Of those who recovered, all but two did so within the first two years, whereas the time needed to obtain optimal improvement was more or less normally distributed around five years. The patients who recovered apparently did so as a direct result of treatment, and no other factor appeared

to play any essential part in the outcome. On the other hand, in the cases of patients who only improved, auxiliary factors were present in addition to adequate treatment, namely, a good preillness personality; a dependable and sympathetic supportive person, usually a close relative, and some kind of occupation. Patients whose condition remained stationary all lacked one or more of these factors, and about half of them lacked them all.

Penicillin in Neurosyphilis.—Dammann and Schmidt [180] record that, in 1950, 12 million units of penicillin G sodium were given in aqueous injections of 200,000 units over a period of 10 days to 29 women and to 19 men with neurosyphilis. Of the 48 patients, 18 had cerebral and cerebrospinal syphilis, respectively; 1 had cerebral gumma; 12 had tabes; 5 had progressive paralysis; 1 had syphilitic meningitis; 1 had syphilitic atrophy of the optic nerve, and 9 had latent syphilis with positive cerebrospinal fluid. Except for a few, these patients did not receive any further treatment up to 1952, when follow-up examinations were performed on 20 of the 48 patients. Pleocytosis and increase of the total protein values had been reduced within six months after the termination of the treatment in most of the patients, and these values had remained low without further treatment. As compared to results of the first examination, six months after the termination of the penicillin treatment, the number of cells was reduced in one additional patient and reduced total protein values were observed in two additional patients. The stained test that had revealed improvement in 17 patients six months after the termination of the treatment did not show any additional improvement. The reaction of the cerebrospinal fluid to the Wassermann test had within half a year after the treatment become negative in two cases, and within two years it became negative in two additional cases. The reaction of the blood to the Wassermann test showed a similar behavior. All the patients stated that they felt better subjectively and that their work capacity was improved. Objective neurological and psychiatric findings were not changed. The authors state that penicillin proved adequate for the treatment of neurosyphilis and metasyphilis. Improvement in the cerebrospinal fluid occurs within the first six months. Normalization of the cerebrospinal fluid within the next one to two years was observed in only a few cases. Comparison of the results obtained with the penicillin therapy in the 48 patients with those obtained in 17 patients who had received combined neoarsphenamine, bismuth, and malaria therapy indicated that the results were of practically equal value. The advantages of the penicillin treatment consist of the simpler application and the much rarer occurrence of complications. The much shorter stay in the hospital required for the penicillin treatment as compared with the combined chemotherapy and malaria therapy is an additional factor in favor of the penicillin treatment. The authors believe that preference should be given to penicillin therapy. Combined treatment with penicillin and bismuth is at present the method of choice.

During the last 10 years. Verjaal [181] treated 10 patients with neurosyphilis in whom the cerebrospinal fluid showed noticeable pleocytosis, increased protein content, and a pathological colloid curve. The clinical pictures varied greatly in these patients. Half of the patients were treated with arsphenamine and bismuth, and the others were treated with penicillin. The results obtained with arsphenamine and bismuth were discouraging, in that only 6 of 14 patients were cured. The results obtained with penicillin seemed more favorable. However, in some of these cases the follow-up period has not been long enough to permit conclusions. Two patients in whom treatment with arsphenamine and bismuth failed were later cured with penicillin. On the other hand, two who failed to respond to penicillin were successfully treated with arsphenamine and bismuth. No relapse or exacerbation was ever observed after the changes in the cerebrospinal fluid had completely disappeared. Cohn [182] reported the results of treatment of 36 patients with syphilitic meningoencephalitis, 18 of whom were treated with penicillin-malaria, and 18, with penicillin alone. Sat-

isfactory clinical results were obtained in 11 patients (61.1%) treated with penicillin-malaria and in 5 (27.7%) treated with penicillin alone. Satisfactory serologic results (33 patients) were obtained in 94.1% of the combined group and in 81.2% of the group treated with penicillin alone. Clinical failure rates were 22.2 and 38.8% for the two groups, respectively, while the serologic failure rates were 5.8 and 18.7%, respectively.

Electrotonic Treatment in Dementia Paralytica.—A report is presented by Petersen [183] of the results of electrotonic treatment (electroshock) in 70 patients with dementia paralytica at the Rochester, Minn., State Hospital. The ages of the patients ranged from 28 to 62 years. There were 53 men and 17 women in the series. Of the 70 patients, 42 improved greatly, 21 improved slightly, and 7 remained unimproved. It is emphasized that the electrotonic treatment was not used primarily for the underlying pathologic condition. It was always followed by fever or chemical therapy or both. Improvement in the cerebrospinal fluid was noted in the majority of patients who had not recently received intensive treatment. In some cases the treatment was lifesaving. Case reports are presented for three of the patients in this series.

Surgical Aspects of Tabes Dorsalis.—According to Lees [184] the surgical aspects of tabes dorsalis are (*a*) the visceral crises, which may produce difficult diagnostic problems; (*b*) urinary symptoms; (*c*) arthropathies. It is considered that most of these are due to involvement of the sympathetic and vagus fibers, especially in the ganglia and rami communicantes, associated with the posterior roots of the spinal nerves. Specific treatment of syphilis and special treatment of symptoms is generally rewarded by a great measure of relief. Prevention of urinary complications or treatment of established "cord" bladder is of lifesaving importance to the tabetic. Tabetics should be kept as mobile as possible to prevent severe ataxia. If ataxia has developed it is possible to reeducate the patient to a very great extent. Arthropathies respond moderately well to conservative orttheopedic procedures; it is occasionally necessary to undertake excision, arthrodesis, or bone transplantation.

Reagin After Treatment of Neurosyphilis.—It has long been known that in patients treated for late neurosyphilis blood serum and spinal fluid tests for syphilis continue to give positive results for varying periods after treatment. Yet many patients are still treated unnecessarily in the hope of reversing such positive reactions. This practice continues because few reports on the long-term follow-up of large series of patients have been reported. A brilliant attempt to correct this defect is made by Evan W. Thomas, [185] with data obtained in a 5- to 14-year follow-up of 181 patients treated for neurosyphilis with malaria therapy and a 5- to 8½-year follow-up of 213 similar patients treated with penicillin. He found that positive results from serologic tests for syphilis persisted in 80 to 84% of patients followed for 5 years and in 70% of patients followed for 10 years after treatment. Positive results from tests for spinal fluid reagin were found in 63% of patients followed for 5 years and in 27.7% of patients followed for 10 years after treatment.

Several patients in each group who had no evidence of clinical relapse or of pleocytosis were retreated for the sole purpose of noting the effect on persistently high blood serum reagin titers. Retreatment in such cases had no significant effect on the titers of either the blood serum or the spinal fluid. Not only in patients with neurosyphilis but also in those with other forms of late syphilis, Thomas proved to his own satisfaction the futility of prolonging treatment or of retreatment for the sole purpose of lowering high reagin titers.

Our present ignorance of the true nature of serologic tests for syphilis is emphasized not only by fluctuations in titers but also by the frequently occurring discrepancies among titers from different tests performed on the same specimen of blood. Wide fluctuations in titers may be reported for one test but not for another, or there may be for years pro-

nounced sustained discrepancies in the titers obtained by different tests. The occurrence of such discrepancies suggests that the reagin tested for in the blood serum is a complex substance that may consist of more than one presumed antibody or that in some persons inhibitory substances interfere with the demonstration of reagin more in some tests than in others. The wide fluctuations in titer following treatment suggest that factors other than syphilis influence the tests in known syphilitic patients as well as in persons who have biologically false positive reactions to tests for syphilis. Whatever the explanation may be for the bizarre serologic patterns noted in a prolonged follow-up of treated syphilitic patients, it is reasonably certain that, in the absence of other evidences of relapse or progression of the disease, they do not indicate continued activity of the syphilitic process, and treatment should not be continued solely on the basis of such serologic patterns.

Study of the spinal fluid did not reveal the bizarre serologic patterns noted in the blood serum of some patients. Consequently, the reagin present in spinal fluid seems to be less influenced by unknown factors than is the reagin in blood serum. When Thomas found the spinal fluid reagin present in relatively large amounts at the time of treatment, the titer invariably fell significantly within six months to a year after treatment, but it frequently remained at low levels for years without evidence of clinical progression. Patients with low spinal fluid reagin titers, when treated, often continued to have low titers for varying periods after treatment. In general, reagin disappears more rapidly from the spinal fluid than from the blood serum, but the reverse may be true.

Persistence of demonstrable reagin in the spinal fluid does not necessarily prove persistence of the syphilitic infection in the central nervous system, and it certainly does not prove failure to arrest the infectious process. Thomas' experience shows that if the spinal fluid cell count has become normal and there has been improvement in the results of other spinal fluid tests for two years after treatment the infection may be confidently expected to have been permanently arrested. At Bellevue Hospital, Thomas never observed relapse of neurosyphilis, as shown by an increased cell count and increases in results of other quantitative tests of the spinal fluid, more than two years after treatment, even though demonstrable reagin was still present.

OCULAR SYPHILIS

Treatment of Syphilitic Optic Atrophy by Penicillin, With and Without Therapeutic Malaria.—In a detailed analysis including post-treatment observation of four to eight years of 37 patients with syphilitic optic atrophy treated with 4,000,000 units of penicillin alone, or with a combination of penicillin and tertian malaria, Kenney and Curtis [186] found no significant difference between the therapeutic effects of penicillin alone and penicillin with malaria. Their findings agree with those previously reported by Klauder and by Moore that when loss of visual acuity is advanced treatment will not prevent progression to blindness. The authors found that the same poor prognosis applies if there is less than 1 sq. in. (6.5 sq. cm.) of visual field area as measured by the planimeter.

Treatment of Interstitial Keratitis with Penicillin, Malaria, and Cortisone (Cortone).—Oksala [187] is in agreement with the majority of workers that antisyphilitic therapy of all kinds, including penicillin and fever therapy, is ineffective in controlling the acute inflammatory manifestations of interstitial keratitis. However, combined penicillin, fever, and local instillation of cortisone caused rapid improvement. He points out that steroid treatment must be continued over a period of many months, because of immediate relapse when it is stopped before the disease has run its natural course. Oksala plans to treat patients with local cortisone alone and believes the results may be just as good as when treponemicidal therapy is given concurrently.

Corticotropin, Thyroid, Testosterone in Syphilitic Interstitial Keratitis.—Klauder

and Meyer [188] report the results of the treatment of 36 patients (56 affected eyes) with acute syphilitic interstitial keratitis who received one or a combination of the following: corticotropin, cortisone, thyroid extract, and testosterone. Systemic use of corticotropin and cortisone was of doubtful value in the severer grades of interstitial keratitis. Extract of thyroid seems to be of some value in therapy of interstitial keratitis. Pyrifer was found to be the most useful means of inducing fever and can even be employed on an ambulatory schedule. Chemotherapy was of little material benefit to patients with interstitial keratitis. The value of testosterone is undetermined.

OTHER THERAPY

Penicillin still holds the fore in the therapy of syphilis, but old and new preparations are constantly being investigated. Keen,[189] for example, feels that, despite modern methods of treating syphilis, potassium iodide is still a useful adjunct in the therapy of osseous syphilis. Hosoya and his colleagues [190] found that trichomycin immobilized T. pallidum of injected rabbits in vitro and was also expected to be active in vivo. Four patients with primary or secondary syphilis and four patients with proved granuloma inguinale were treated by Dunlop and Robinson [191] with daily intravenous injections of 0.5 gm. of oxytetracycline (Terramycin) for 10 days. In the syphilitic patients, disappearance of treponemes on dark-field examination was slow and healing of lesions was slow. One of the four patients relapsed, and only one was seronegative at the end of the observation period, which ranged from 90 to 220 days. Two of the four patients treated for granuloma inguinale relapsed during the observation period. The authors conclude that this schedule of treatment is ineffective both in syphilis and in granuloma inguinale.

Alexander and Schoch [192] found erythromycin in usual dosage to be ineffective in gonorrhea, granuloma inguinale, and lymphogranuloma venereum. However, in four patients with primary or secondary syphilis treated with 200 mg. of erythromycin four times a day for eight days, dark-field examinations became negative in 24 to 30 hours and reduction in the serologic titer was noted in from three weeks to five and one-half months. The authors consider erythromycin effective in the treatment of early syphilis.

TOXIC REACTIONS TO PENICILLIN TREATMENT

Penicillin was hailed at the time of its introduction into medical practice as a preparation of remarkable therapeutic powers and productive of infrequent and trifling reactions. According to Kern and Wimberley,[193] today it heads the list of medicinal agents in the frequency, diversity, and severity of the sensitivities which it induces. In current experience, it has replaced foreign sera as the commonest cause of fatal anaphylactic shock. It is responsible for a growing number of deaths due to irreversible vascular allergy, periarteritis nodosa. Since many of these sensitivities are avoidable and since, in contrast to the usual experience in drug allergy, the most severe sensitivities can be recognized by skin tests, Kern and Wimberley stress the growing need for preventing unnecessary sensitivity, describe the ways in which sensitivity manifests itself, and discuss the management and prevention of the serious and fatal reactions. This paper is of such fundamental importance that every physician using penicillin should read it thoroughly before administering another dose of this useful but potentially dangerous medicament.

Anaphylactic reactions (fatal and otherwise) have been noted to a variety of penicillin compounds. For example, Grekin and O'Brien [194] observed two cases from benzathine penicillin G (Bicillin). Sterling [195] observed nine instances of anaphylactic shock in persons with asthma due to penicillin G or penicillin procaine. Pick and Patterson [196] encountered a case of fatal anaphylactic shock from penethamate hydriodide (Estopen). This patient, too, was an asthmatic. Bell's [197] patient died suddenly from shock after penicillin G procaine. Fein [198] observed anaphylactic reaction from penethamate hy-

driodide (Neo-Penil). Greenfield [199] noted anaphylaxis to intramuscular injection of penicillin in oil. Several members [200] of the Food and Drug Administration (Department of Health, Education, and Welfare) conducted a survey at a number of large hospitals in scattered metropolitan areas in order to furnish some indication of the extent of reactions of penethamate, but all antibiotics were included. They concluded as follows: 1. Injectible penicillin is more prone to cause anaphylactoid reactions than is oral penicillin. 2. Although the incidence of anaphylactoid reactions has increased in frequency during the past few years, it is still relatively infrequent when consideration is given to the tremendous tonnage of penicillin distributed annually. 3. Patients with a history of bronchial asthma, hay fever, and other allergies or previous sensitivity to penicillin are more prone to exhibit anaphylactoid reactions. 4. The seriousness of anaphylactoid reactions emphasizes again the importance of having a clear-cut indication for the use of the drugs. In those patients with a history of bronchial asthma, hay fever, or other allergies, the physician must balance the hazards involved against the extent and nature of the disease being treated. 5. Penethamate has an inherent toxicity, which can be controlled only by the use of proper dosage.

Severe Reaction to Penicillin.—Sohval [201] reported an alarming reaction that occurred in a patient immediately after intramuscular injection of an aqueous suspension of penicillin procaine. The reaction pattern did not conform to either of the two previously described major types of immediate reaction, i. e., (1) an anaphylactic-like shock state and (2) nonallergic reaction characterized by sudden weakness, angor animi, no recognizable evidence of hypersensitivity, and neither circulatory nor respiratory disturbance. The reaction pattern in Sohval's patient is difficult to classify. He suffered no shock, no dyspnea, no sweating, and no disturbances of consciousness; on the other hand, he had vertigo, transitory hemiparesis, an odd metallic taste in the mouth, sense of thoracic compression, sense of nasal obstruction, and severe palpitations. The patient also displayed intense anxiety and fear of impending death, accompanied by a staring expression. No medication was administered. Recovery from the alarming phase of the reaction was complete in 15 minutes, although a feeling of fatigue persisted for a day.

Unusual Complication of Therapy.—Fairlie and Kendall [202] detailed three autopsied cases of fatal Staphyloccus enteritis. These occurred after prophylactic use of penicillin and dihydrostreptomycin. Recovery from what appeared to be an identical condition was observed in two cases in which the antibiotics were discontinued promptly. Fairlie and Kendall state that the concept that this complication is due to suppression of normal intestinal flora permitting pathogenic overgrowth of intestinal staphylococci appears to be oversimplified. They feel that a direct stimulation of the Staphylococcus by antibiotics must be considered. Fever or diarrhea appearing in a patient receiving antibiotics should immediately suggest this complication. The primary therapeutic measures are prompt discontinuance of antibiotics and attention to fluid and electrolyte balance.

Cutaneous Reactions to Penicillin.—Katzenellenbogen [203] encountered 13 cases of cutaneous reaction to penicillin within a four-week period. He states that the possible causes of so many penicillin reactions in a short period include (1) previously or currently existing mycosis, (2) indiscriminate use of penicillin ointment, lozenges, etc., (3) the allergic condition of the patient, and (4) the brand of the drug. The author recommends avoiding the local use of penicillin or its injection without proper indication. It is suggested that in suspected cases antimycotic and antihistaminic treatment be given at the same time as the penicillin injections. Cortisone was helpful in severe cases of delayed serum sickness.

Procaine Amide in the Treatment and Prevention of Penicillin Reactions.—Two comparable groups of patients with allergic reactions to penicillin were treated by Jennings and Olansky [204] with procaine amide

hydrochloride (Pronestyl) and diphenhydramine hydrochloride, U. S. P. (Benadryl), respectively. They found procaine amide hydrochloride as good as and probably better than diphenhydramine hydrochloride in treating such cases. They found procaine amide hydrochloride of value in 13 of 18 patients in prophylaxis of allergy in known reactions to penicillin.

Desensitization of the Penicillin-Sensitive Patient.—Alexander [205] presented a report of the desensitization of four persons who had become sensitive to penicillin and for whom penicillin therapy subsequently became necessary or imperative. The four persons were (1) a white male nurse aged 60 years whose sole duty was the administration of penicillin to patients in syphilis wards; (2) a white man aged 64 years with late syphilis of the pharynx; (3) a white man with syphilitic meningitis, and (4) a Negro aged 64 years with untreated cardiovascular syphilis (aortic regurgitation). The four patients were desensitized by the intramuscular administration of graded doses of penicillin, two with aqueous penicillin (Cases 1 and 3), one with delayed-absorption penicillin (Case 2), and one with aqueous and delayed-absorption penicillin (Case 4). The intramuscular route seemed to be the logical one to use, since penicillin in therapeutic doses is usually administered intramuscularly. In desensitizing regimens, the important factor is keeping the desensitizing doses below the reaction level of the patient's sensitivity. In an addendum the author states that since the paper was submitted for publication four additional patients were desensitized.

Use of Cortisone During Penicillin Treatment of Secondary Mucocutaneous Syphilis in a Hypersensitive Patient.—Brodey and Nelson [206] report a case of infectious secondary (late recurrent) syphilis treated simultaneously with cortisone and penicillin. Cortisone was given to control the severe symptoms of hypersensitiveness to the antibiotic. It appears that cortisone may be employed safely in situations of this sort if large doses of penicillin are given at the same time to control the syphilitic infection.

TOXIC REACTIONS NOT DUE TO PENICILLIN

Osgood,[207] long a student of such matters, has reviewed the problem of drug-induced hypoplastic anemias and related syndromes. Fortunately some of the antisyphilitic drugs classed among the high-risk preparations are either but little used or are on the way out of the syphilotherapeutic armamentarium. Snively and his co-workers [208] have reported a case of aplastic anemia (depression of bone marrow) following the use of corticotropin. Fulminative sepsis caused the fatal termination. A case is reported by Edmunds [209] in which organic arsenical therapy was followed by both aplastic anemia and severe hepatitis, probably due to the virus of homologous serum jaundice. Pocock [210] made a study to evaluate the concept that postarsphenamine jaundice represents homologous serum hepatitis and to clarify the role of arsenic-containing compounds in the causation of hepatitis. He utilized 47 cases of jaundice seen in the syphilis clinic of Vanderbilt University Hospital during the years when arsenic-containing compounds were being used. He demonstrated the early and late occurrence of jaundice and presented evidence indicating that cases of the late type were probably homologous serum hepatitis. He also details certain factors involved in the nonrecognition of the true nature of these cases.

SYPHILOID DISEASES

The world effort to combat the treponematoses has not abated. As a result, material progress continues, and this should set an example to local governments of what individual and mass treatment and control programs can do even under the most primitive conditions. Much material of similar nature by the same workers was reviewed in the last edition of this annual series. The bulk of the present reports deals chiefly with yaws.

The Treponematoses.—In this paper, which was presented before the Royal Fac-

ulty of Physicians and Surgeons in Glasgow, Feb. 11, 1953, Willcox [211] reviews the literature on the various nonvenereal treponematoses (yaws, pinta, and endemic syphilis) present in the world today. These are described and compared, and treatment measures are discussed. The author states that these diseases are symptomatic of social conditions which existed in this country centuries ago and are primarily a social rather than a medical problem. When children are taught to don clothes, the nonvenereal treponematoses die out. Monnerot-Dumaine [212] also reviews briefly some of the present knowledge of the treponematoses: bejel, yaws, and pinta. He adds a short commentary on the general conception of the treponematoses. He does not favor the unitarian view of these processes. A statistical analysis of 45,000 admissions to a clinic in West Africa during the fiscal year 1949-1950 by Poindexter [213] showed that 28% of the patients gave clinical or serologic evidence of treponemiasis, 95% of which consisted of yaws due to T. pertenue; 17% had leucorrhea or nongonorrheal urethritis; 17% had Trichomonas vaginalis; 6% had one or more venereal diseases, with gonorrhea making up about 80% of the group.

Role of World Health Organization in Yaws Control.—Bonne and his co-workers [214] indicate that international cooperation of health work is not new; however, in 1950 modern therapeutic methods first began to be applied on a mass scale. WHO is particularly interested in yaws, because it is a major public health problem in many countries and because repository penicillin is a simple weapon of high therapeutic efficacy with which to combat the disease. If mass treatment is carefully planned and systematically carried out, the immediate result will be a significant reduction in the prevalence of infectious cases. Only time will tell whether the disease can be permanently effected by mass treatment. Results will depend upon how well governments consolidate the gains and integrate the work into the public health structure of their countries. The contribution of WHO does not exceed that of the government. Governments, while stimulated and assisted by WHO, are ultimately responsible for the solution of their own health problems.

Role of United Nations International Children's Emergency Fund in Yaws Control.—UNICEF, according to Keeny,[215] is interested in the control of yaws because the disease affects millions of children. The policy of UNICEF is to concentrate its assistance on a few diseases which are widespread. In three years the partnership between WHO, the body responsible for coordinating health programs throughout the world, and UNICEF, the body providing supplies, has led to the development of 100 projects in Asia alone. Money used by UNICEF is provided by voluntary contributions, of which approximately 90% comes from governments. The cost of treating one patient with yaws has been approximately $2.50. It is believed that the 10,000,000 cases of yaws in southeast Asia can be effectively controlled in 10 years.

Nonspecific Factors in the Epidemiology of Yaws.—Nonspecific factors in the epidemiology of yaws that are discussed by Hill [216] involve the host and his environment. Such factors as temperature, altitude, rainfall, geologic formation, and humidity play a part in the incidence of the disease. Yaws flourishes in hot climates and where there is an annual rainfall of over 50 in. (125 cm.). Incidence is higher where the soil is impervious and drainage is poor. High humidity is responsible for a sogginess of the skin and an increase in the incidence of skin infections from fungi and other organisms. Yaws is endemic where standards of living are low and where there is overcrowding and lack of proper sanitation and facilities for personal hygiene. There is no apparent connection between dietary deficiency and yaws incidence. There is no racial immunity. More males than females acquire the disease. Evidence that syphilis is rare in regions where yaws is endemic suggests that there is some cross immunity between the two diseases.

Diagnostic Aids in Mass-Treatment Campaigns Against Yaws.—Rein [217] again insists that serologic laboratories should play an important role in mass treatment campaigns against yaws; however, facilities for satisfactory serodiagnosis are usually least adequate in areas with the greatest prevalence. In high-prevalence areas it is feasible to treat the entire population without serologic examinations, while in low prevalence areas it is necessary to conduct careful serologic examinations with tests known to have high levels of sensitivity and specificity. The filter paper method and modifications of the Chediak reaction have not proved of sufficient sensitivity or specificity when compared with the standard tube or slide tests. A well-controlled laboratory should be set up in the pilot area, regardless of whether serodiagnosis is used in the mass-treatment area. The laboratory should determine the disappearance time of treponemes from lesions by dark-field microscopy. The serologic trend following therapy should also be determined by quantitative serologic tests carried out before treatment and at three-month intervals for one year after treatment.

Principles and Practice of Yaws Control.—In this review, from the Wellcome Museum, London, of the principles and practice of the control of yaws, it is first pointed out that the object of an antiyaws campaign is not merely the reduction of the incidence of yaws to some ill-defined low endemic level but the complete eradication of the disease by the recognition and treatment of all infectious and potentially infectious patients, including contacts and patients in the latent secondary stage. Recognition depends on a careful survey of the whole population by trained local medical auxiliaries. In countries in which the rural population lives in large villages or small villages close together, one suitably placed center is established, but where the population is scattered house-to-house visits must be made. Treatment is given in a single intramuscular injection of penicillin procaine in aluminum monostearate (PAM). Adults received at least 1 to 2 mega units and children proportionately less; the dose given to contacts is half that given in the infectious stage of the disease. Hackett [218] suggests that until some means of detecting the latent stage of yaws has been evolved treatment must be given to (1) every person who has had active secondary lesions during the preceding five years or (2) every person under 18 to 20 years of age or (3) all school children and children aged 2 to 6 years who have yaws or who have a history of yaws. Measures designed to prevent the reintroduction of the disease into an area already controlled are an essential part of the program. Rural dispensaries, with an itinerant staff and facilities for seeking out cases and for treatment, must be maintained to deal with the few cases that occur after the initial campaign is over. The work of these dispensaries can be extended eventually to include treatment for malaria, bilharziasis, and worm infestation. The author emphasizes the importance of obtaining the cooperation of the inhabitants and their leaders throughout the campaign.

Yaws in Brazil.—Guimaraes [219] believes that yaws was probably introduced into Brazil by Africans shipped in the 17th century as slave labor for the sugar cane plantations. The rains and the humidity are most important factors in the epidemiology. In all, the agricultural laborers are the most prone to develop the disease, but in the northeast and the east it is in the sugar cane areas that the population suffers most. In the zones where yaws exist the fly of the order Diptera is abundant. Yaws patients believe that these flies transmit the disease. Greatest incidence occurs in the 9 to 20 age group. Negroes and mulattoes represent about 70% of the total number of cases. Brazil has no special service with a national program for combating yaws. Responsibility rests with the Sanitary Organization Division of the National Department of Health, which maintains rapid-treatment centers and posts.

Planning for Yaws Control in Southeast Asia.—Jungalwalla [220] states that plans for yaws control in Indonesia and Thailand had to be fitted into the framework of the existing

public health services. Areas selected as bases from which the work would be carried out had to provide facilities for administrative and supply services and also serve as training and demonstration centers. Work was planned as a mass campaign, including surveys, diagnosis, treatment, and resurveys. It was estimated that 15% of the Indonesian population had yaws and that 4.8% in Thailand had the disease. Speed of work was estimated at 1,000 persons per month by each team member in areas where no house visiting was done and where the population was not scattered. The aim of the campaign in Southeast Asia has been to set up a system capable of being continued as part of the normal health structure.

Extent and Nature of the Yaws Problem in Africa.—Yaws is most prevalent in Africa in the zone 10 degrees north and 10 degrees south of the equator, according to Hackett.[221] Incidence is highest in humid areas, where vegetation and water are abundant and where the population is relatively dense. Yaws is usually contracted in childhood. Secondary lesions are most frequent in children and adolescents, while tertiary lesions are most frequent after puberty. Infectious lesions are infrequent after the age of 30 years. Distribution between sexes is approximately equal. There are no records or evidence of the occurrence of cardiac, ocular, or central nervous system lesions. Investigations of two outbreaks in mines in the Union of South Africa showed that transmission was by close bodily contact underground in the hot humid atmosphere. Data presented in this paper were based on replies to a questionnaire distributed throughout Africa. Willcox [222] reports that in Africa a treponemal infection is seen in a number of areas which is nonsexually transmitted in childhood, like yaws. He feels that this disease is similar to bejel, which is endemic in Iraq and Syria. Because of the high incidence of chancroid in Africa and the difficulties of differentiating chancroid from primary syphilis, because of inadequate diagnostic facilities, Willcox emphasizes the need for a single therapeutic modality which will be effective against chancroid as well as against the treponemal diseases. In experimentally inoculated chancroid, neoarsphenamine, antimony, and bismuth were found to be ineffective, while sulfonamides, penicillin, streptomycin, chlortetracycline, and chloramphenicol were found to be effective. In clinical infections a single dose of 2,400,000 units of penicillin procaine with aluminum monostearate healed 85% of patients with chancroid. Willcox concludes that penicillin is sufficiently effective in chancroid that it may properly be used in a mass-treatment campaign.

Yaws-Control Program in India Expanded.—The yaws control measures begun late in 1952 in Madhya Pradesh, India, have been extended to Hyderabad and Madras States.[223] Expansion inMadhya Pradesh is also planned in an effort to bring yaws under control in an area of approximately 50,000 square miles. This control program in India is part of a five-year plan for improving the status of tribal groups. The entire campaign is the responsibility of the respective State Governments, but WHO is providing technical guidance and UNICEF is providing penicillin and other essential supplies and equipment.

Experience with Yaws Control in Indonesia.—Soetopo and Wasito [224] report that attempts had been made to control yaws in Indonesia for 30 years. In 1951 a new approach was developed with the objective of screening as close to 100% of the population as possible. Treatment was to consist of two injections of PAM. In the first area where the program was used, 87.2% of the entire population was examined. The average prevalence found during the initial survey was 10.2%. A follow-up showed that the cure rate was 93%. Results of the survey showed that the 3- to 10-year age group had the highest percentage of infectious cases.

Effectiveness of Penicillin in Treatment of Yaws.—Sepulveda and Ibarra [225] review the literature and describe the various stages of yaws. A report is presented of the treatment with penicillin of 56 patients with yaws in

1950. Of the 56 patients, 36 were male and 20 were female. The majority of the patients (52) were between 3 and 14 years old. The youngest was 3 years old. There were 28 patients with secondary lesions only, while the other 28 had both primary and secondary lesions. A total dose of 900,000 units of penicillin G procaine in oil with 2% aluminum monostearate (PAM) was given to 30 patients, of whom only 16 were followed. A total dose of 1,200,000 units of PAM was given to 26 patients, and of these only 10 were followed. Excellent clinical results were obtained, but the serologic results were unsatisfactory. Of the 26 patients who were followed only 3 attained seronegativity for the first time from 3 to 15 months after treatment. Results of this study are compared with reports of previous studies. Penicillin is considered the drug of choice in the treatment of primary and secondary lesions of yaws, causing rapid desiccation of the lesions, regardless of the dosage.

Time-Dosage Relation in Penicillin Therapy with Special Reference to Yaws.—According to Kitchen and Rein,[226] the discovery, development, and intelligent use of any specific therapeutic agent necessitate an orderly sequence of studies of its toxicity, pharmacologic action, and clinical effectiveness. Selection of schedules in the treatment of yaws with penicillin depends upon accurate laboratory determinations of the relation between the concentration of the drug in tissues and circulating fluids and its bactericidal effect. No consistent variation in the susceptibility to penicillin of the treponemes of venereal syphilis, endemic syphilis, yaws, or bejel has been noted. Both in vitro studies and therapeutic experience have indicated that the demonstrable sensitivity to penicillin of T. pallidum is also applicable to T. pertenue. Inconclusive results of early studies on the efficacy of penicillin against treponemal diseases may be attributed to the shortage of the drug and the time-dose relation.[227] A series of clinical studies was made to determine the efficacy of penicillin therapy in yaws, syphilis, and pinta. Treatment schedules were selected that would ensure the proper time-dose relation so that adequate therapeutic levels were maintained for 96 hours. Clinical results with repository penicillin were consistently good in the studies made in the treatment of yaws in Haiti, of pinta in Mexico, and of early syphilis in New York. With a satisfactory preparation of penicillin, adequate therapy can be given in a single injection.

Treatment of Yaws with Benzathine Penicillin.—The possible use and usefulness of new long-acting penicillin salts in mass campaigns are currently under investigation in an international research scheme coordinated by WHO, and a preliminary report on the results of treatment of 236 patients in a rural area in Thailand with benzathine penicillin has been published. The patients represented two diagnostic groups, one with infectious yaws and another with palmar and plantar hyperkeratosis, and two treatment schedules were used, namely 0.6 and 1.2 mega units administered in a single injection. No difference in outcome between the two schedules was observed, and the resulting clinical and serological effects after six months were satisfactory. The by-effects (Herxheimer type of reaction with fever and with pain at the site of injection) experienced by the patients in this series appeared to be more frequent than those reported in the treatment of early syphilis with this penicillin salt; it should, however, be noted that the fever reactions were not recorded by temperature measurements. Grin and his co-workers [228] point out that the preparation and administration of aqueous suspensions of benzathine penicillin by auxiliary personnel under field conditions in rural areas proved to be more complicated than using "ready-to-inject" PAM. This may possibly limit its use in mass campaigns, but further trials are expected to provide more information on this point.

Treatment of Infectious Yaws with One Injection of Penicillin.—In a report by Levitan and his colleagues [229] it is shown that of 636 patients treated for yaws in Haiti 358 received 600,000 units of a penicillin-aluminum monostearate preparation which failed

to maintain a satisfactory blood level, while 221 patients received 600,000 units of a satisfactory PAM preparation. Another group of 57 patients received only 300,000 units. Among the patients observed for more than six months, satisfactory results were obtained in 100% with primary yaws, in 90.5% with secondary yaws, and in 89.7% with wet crab yaws. There were only four relapses or reinfections, and these were in patients who had received the unsatisfactory preparation. A dosage of 600,000 units appeared to be adequate for mass treatment.

Antibiotics Other Than Penicillin in Treatment of Yaws.—Chlortetracycline, chloramphenicol, and oxytetracycline appear to be equally efficacious in the treatment of yaws. Results of trials in Jamaica, by Hill,[230] involving the treatment of about 200 patients by oral administration of the drugs, showed that the ideal treatment was a course of two intramuscular injections. Tables of results of treatment by various authors using the antibiotics are shown. Clinical cures were obtained by each in most instances.

Clinical Aspects of Bejel.—Csonka [231] has detailed, in a well-documented report, some clinical and epidemiological aspects of bejel, a nonvenereal treponematosis found among the rural Arab population of some Middle-Eastern countries, on the basis of 3,507 cases seen in Iraq under the auspices of the bejel campaign sponsored by WHO/UNICEF. The infection commonly, though not exclusively, affects children and adolescents of both sexes and imitates closely the secondary and benign tertiary stages of venereal syphilis. It involves mainly the mucous membranes, skin, and bones. Primary lesions were found only in exceptional circumstances, and in the present material no obvious cases of neural or cardiovascular involvement came to light, but such visceral complications remain a possibility. No evidence of congenital transmission was found; the apparent similarity of certain features with congenital syphilis is discussed. The "natural history" of untreated bejel is suggested on the basis of a clinical cross section of over 3,500 consecutive cases. The relationship of bejel to syphilis and other treponemal diseases is still uncertain, but in practice it responds, like all the others, to penicillin. The first results with the newer antibiotics are satisfactory, though penicillin remains the drug of choice for mass treatment. The raising of hygienic standards in the bejel areas is considered essential to consolidate the good early results achieved by mass treatment with penicillin. Jones [232] has reported a case of "mutilating" bejel in a 16-year-old Iraqian youth. The cutaneous gummatous lesion affected the center of the face (complete destruction) and the trunk (chest wall and upper abdomen). The left tibia showed the sabre appearance of osteoperiostitis.

CONTROL OF SYPHILIS

According to Cowan and Shaw,[233] one of the most dramatic episodes in modern epidemiology has been the decline in the reported incidence of syphilis. Primary and secondary syphilis in Michigan declined from 79 per 100,000 in 1946 to 4 per 100,000 in 1952. Reported cases of gonorrhea were 117 per 100,000 in 1952, in comparison with 231 per 100,000 in 1945. Venereal disease is becoming a problem of the private physician rather than of the public clinic. Major responsibilities for the future are the control of the spread of the disease and the prevention of late sequelae or catastrophic results of untreated syphilis. A real decline in venereal disease can be proved only by an equal or greater number of diagnostic observations which result in a smaller number of positive diagnosed cases. The following statement in *Public Health Reports* [234] is typical of current opinion:

> The downward trend in both syphilis and gonorrhea case rates, begun following World War II continued during the fiscal year 1953. However, smaller decreases in annual case rates from 1952 to 1953 as compared to previous years indicate a current tendency for these rates to level off. If this tendency continues, it will not be long before the rates cease to decline.

In an analysis of syphilis mortality throughout the United States in the period 1939 through 1948, Usilton and her co-workers [235]

found a 47% reduction in the crude syphilis mortality rate during this period. However, in 1948 syphilis ranked third among the infectious diseases as the cause of death, being topped only by pneumonia and tuberculosis. Syphilis mortality is greater among men and among nonwhites than it is among women and the white population. The death rate was higher in the South through the entire period of study. It was emphasized that, in view of the aging of the population, it is essential to compute age-specific death rates in order to appreciate fully the reduction in syphilis mortality. The annual report of the Chief Medical Officer of the Ministry of Health for 1952 [236] states that, compared with those for 1951, rates in both acquired and congenital syphilis were lower. Rates in gonorrhea were higher. The comment was made that, in spite of penicillin and other antibiotics, venereal urethritis, both gonococcic and nongonococcic, has increased during 1952. This fact should restrain any tendency to complacency about the venereal disease situation. What has occurred with gonorrhea might yet happen with syphilis.

Stability of sexual relations depends, among other things, according to Marcussen,[237] on environment, social circumstances, and cultural level and may vary in accordance with geographic and social conditions. Less stable sexual relations are considered to be those with one or a few casual contacts, including pick-ups, prostitutes, and chance acquaintances. All other types of sexual relations are considered to be stable. The hypothesis that relatively stable sexual relations are more favorable to the transmission of syphilis than to transmission of gonorrhea gives an explanation of the observation that the population of some islands, where sexual habits differ from those of European people, are subject to infection with gonorrhea and syphilis is less prevalent. It may also explain various facts concerning marital contagion and infection among sailors during local epidemics.

Costs of Untreated Syphilis.—An editorial in the *Journal of Iowa State Medical Society* [238] states that, on the basis of the estimate that there are 2,100,000 cases of untreated syphilis in the United States, Iowa's portion is 0.9%, or 18,900 cases. At $2,246 per capita per year, it is estimated that an income loss of $73,565,484 would result. Maintenance of persons in tax-supported mental institutions with psychosis due to syphilis is estimated to cost $768.00 per person per year in Iowa. Paretics and those with meningovascular syphilis with psychosis can be expected to number 25 cases per 1,000 cases of syphilis not found and have an average stay of 10 years in these mental institutions. This would result in 472.5 such cases, who would spend a total of 4,725 years in institutions at a total maintenance cost of $3,628,800.00. In September and October, 1952, a mass survey of 19,344 persons was made by Wilzbach,[239] in Cincinnati, Ohio, in which 8.8% of the tests were found to be positive. The fact that 1,150 cases of the 1,683 with positive samples had not been known to the health department indicated that there was more syphilis in the community than reports to the health department showed. There was also evidence that a large number of persons with syphilis are not discovered until the disease has become latent, which indicates a need to discover ways and means of finding primary syphilis. Fiumara [240] states that present-day control methods will not eradicate the venereal diseases. The diagnostic and treatment care at the present time and in the future should be geared to ambulatory medical care. Outpatient centers of general hospitals should be utilized for the care of the medically indigent. Contact interviewers and investigators will have the opportunity to interview their patients. With proper control methods, the venereal diseases can be brought down to that irreducible minimum that is a practical goal for public health administration.

Half a Century of International Control of the Venereal Diseases.—Prior to 1910 venereal disease was not considered an international problem.[241] By the time the Health Organization of the League of Nations came into being, syphilis was recognized as a widespread health problem. The International

Union Against the Venereal Diseases began its work just after World War I. The League and the International Union participated in a movement to provide venereal disease control services for merchant seamen, which resulted in the Brussels Agreement of 1924. Since World War II, the keystone of international venereal disease control has been the venereal and treponemal disease program of WHO. WHO's approach to control—to aid, to the extent of its resources, in the immediate diminution of disease in areas of greatest need and at the same time to assist in building permanent public health structures, especially through training of native personnel—makes bright the hope that effective worldwide control of venereal and treponemal disease can be accomplished.

Epidemiology of Venereal Diseases.—Johnwick [242] maintains that syphilis and gonorrhea are an epidemiologic entity. Although they differ clinically and etiologically, they cannot be separated epidemiologically. Most women or men who have venereal diseases are equally promiscuous. No person who acquires either syphilis or gonorrhea knows beforehand which of the two he will acquire. A person who decides to be promiscuous exposes himself to a risk from syphilis or gonorrhea which can be expressed as a ratio of the contemporary reported incidence of the two diseases. The venereal disease reservoir exists in a small proportion of the population group of 15 to 40 years. The same age-race-socioeconomic segment of the population furnishes most of the new recruits to the venereal disease reservoir each year.

Venereal Disease Control and Prevention.—Fuimara [243] points out that the foundation upon which the venereal disease control program rests is early diagnosis and treatment. Reductions in prevalence are the result of an efficient and organized control program and the effect of penicillin in rapidly reducing gonorrhea and syphilis infection. The problem of prevention is one of controlling promiscuity. If the program is to be effective, efforts must be directed towards motivating and modifying human sexual behavior to socially and ethically accepted standards.

Contact Interviewing and Investigation.—Contact interviewing is a profitable means of finding new cases of venereal diseases.[244] Tact, patience, understanding, pleasant mannerisms, a professional attitude, and a definite liking for people are the necessary components of a good contact interviewer and investigator. Three methods of contact interviewing are the sex history approach, educational approach, and a combination of the two methods. The epidemiologist is responsible for the follow-up of patients who have lapsed from observation and treatment. The generalized public health nurse and the clinical nurse have a vital role to play in the field of both prevention and control of the venereal diseases.

Report of the Study Group on Syphilis.—The study group of the Sixth World Health Assembly [245] agreed that the following points should be emphasized: Penicillin has revolutionized the outlook of public health programs against the treponematoses. Use of large doses of PAM permits rapid elimination of the reservoir of infection, and adequate treatment can be achieved in a short period of time. The shortening and simplification of treatment have rendered case-finding and follow-up of patients for post-treatment control more complicated. In long-term programs, health education and an effort to increase understanding and social responsibility will facilitate early diagnosis and treatment. Syphilis remains a disease of international importance because of the increasing amount of international travel. The long-term outlook does not justify any relaxation of vigilance or abandonment of special efforts against syphilis through general or selective health programs.

Case-Finding Through Multiple Screening.—Among more than 1,000,000 persons screened by nine major projects, Kurlander and Carroll [246] report that approximately 50,000 cases of disease and/or abnormalities have been identified. Eight of the nine projects used serologic tests for syphilis. Among

the approximately 750,000 persons tested, about 39,000 cases of syphilis were uncovered. More than a quarter of these were new cases. Of course the question of false reactions, both negative and positive, have to be kept in mind in interpretation of these data.

Serologic Surveys.—Lee [247] noted that a sizable reservoir of syphilis cases in need of treatment is still present in the general population. More effort is required to find them than heretofore. Selective serologic testing of suspected high-prevalence groups will yield considerable numbers of syphilis cases, most of which will fall into the late syphilis category. Serologic testing discovers inadequately treated patients as well as those who have never received treatment. Locating inadequately treated patients must be considered an important gain, as they are as likely as untreated patients to become disabled or a burden to the community. While late complications of syphilis are decreasing in prevalence, there are still substantial numbers of patients who present physical signs and symptoms of progression of the disease. Practical methods for preparing and organizing the community for mass testing programs are presented in a study by Mason.[248] He points out the importance of intangible satisfactions and feelings of security and achievement, in addition to the usual measure of success in mass testing—the number of persons tested. On the basis of a wide experience, important factors in setting up and carrying out a testing program are set forth. The need for leadership, not only from "big names" but also from persons in those groups in which a high incidence of disease is expected, is emphasized. Prostitutes, prizefight managers, and beer parlor and night club operators have been found to be of significant value in organizing segments of the community for mass testing.

Premarital Health Examination. — The premarital health examination attempts to prevent the transmission of syphilis to either party and to the prospective progeny and, by discovering new cases of syphilis, to facilitate case-finding.[249] Premarital laws are meant not to prevent marriages but only to postpone marriages until such time as the infected parties have had adequate treatment or have passed the communicable stage of syphilis. As early as 1913 many states had passed laws regarding premarital physical examinations, but these statutes were inadequate, with no enforcement measures and no penalties for noncompliance. It was not until 1935, when Connecticut passed a law requiring a blood test for syphilis and physical examination, that the pattern for premarital legislation was set. Also, the following year Surgeon General Thomas Parran relaunched his drive against venereal disease. However, there was heated opposition from physicians, who claimed that many serologic tests for syphilis were unreliable and that premarital laws were a threat to the liberty of the individual and the professional secrecy of the physician. It was soon realized that public education was needed if the laws were to work. This was accomplished by newspaper articles, letters and pamphlets to private physicians, and the utilization of the enthusiasm and interest of nonprofessional civic groups. Of the 631,206 blood tests made from 1936 to 1941 in 13 states, 8,605 (1.4%) were found to be positive for syphilis. Many of the positive reactors were unaware of the infection prior to getting a blood test. In New Jersey, of 20,202 tests performed in the State Health Department laboratory during a nine-month period in 1936, 226 persons had positive premarital blood tests. Of 206 persons who were followed, 93 were granted marriage certificates because, in the opinion of the examining physician, the disease was not communicable and 113 were refused certificates to marry. As the implications of positive blood tests became known, the rate of positive reactions dropped suddenly, and it was believed that many people suspecting that they might have a positive serologic test for syphilis were avoiding examination and avoiding the statute by various devices. During the first six months the legislation was in operation in West Virginia, in 1939, positive blood tests were found in 4.2% of 1,600 persons examined; in the next 12 months this per-

centage dropped to 2.4. There was also evidence that enactment of the law caused a decline in the number of marriages in the state in which the legislation was passed. In Connecticut the marriage rates for the two years preceding the enactment of the law (1935) were 7.1 per 1,000 population. For the next three years the rates dropped to 6.8, 5.9, and 6.4, respectively. Premarital laws were simple in operation for residents of the particular state, but certain stipulations of some laws caused difficulty for out-of-state residents. Today, 27 of the 40 states having premarital examination laws will accept the reports of out-of-state physicians and 37 will accept results of out-of-state laboratories. The majority of these laws require that the prospective bride and groom have a physical examination, including a blood test for syphilis, prior to issuance of a marriage license. Those states which do not have such a law are Arizona, Maryland, Minnesota, Nevada, New Mexico, South Carolina, and Washington. The District of Columbia also has no such statute.

Most states with a premarital law have penalties for falsification by any of the parties concerned, but the difficulties of enforcement make the value of such penalties doubtful. Common-law marriages are outlawed in most states, and so evasion through that method now is practically eliminated. Though the constitutionality of premarital health legislation has been challenged, it has been held valid in several court cases. The premarital health examination law augments other legislation pertaining to venereal disease control. Proper legislation and enforcement of laws are necessary to maintain a smoothly functioning control program. Regulatory laws are necessary to insure reporting, adequate treatment, quarantine, and follow-up of persons with venereal disease. During the 12-year period 1939-1951, Condit and Brewer [250] report that more than 2,000,000 premarital examinations were made, which resulted in the discovery of 8,106 previously untreated cases of syphilis and an additional 2,977 previously known cases who were in need of further therapy. The number of premarital examinations has declined about 23% from the peak in 1946 to 1951, while during the same period total reported cases of syphilis have declined 63%. In view of these trends it appears that the efficiency of the premarital examination law as a screening technique has diminished during this period.

The Syphilis Problem in Asir Province, Saudi Arabia.—A report by El Ghouroury [251] on combined national and international venereal disease team activities in the province of Asir has been published by WHO. Several groups of the population were examined—namely, (1) army personnel, (2) police force personnel, (3) persons attending the outpatient clinic at the local hospital, (4) the inhabitants of various quarters of Abha by house-to-house visits, and (5) the inhabitants of some of the surrounding villages. Serological tests were made on 2,359 blood samples, and a total of 309 patients were given complete clinical examination and treatment with PAM in doses varying from 2,400,000 to 6,000,000 units. A review of the results obtained showed that certain clinical and epidemiological features were apparent: Only one primary lesion was found; secondary lesions were rather common, amounting to 5.8% of all cases treated, and tertiary lesions represented 12.6% of all cases treated and 67.2% of all clinical cases. Considerable variations in the prevalence of syphilis were noted among the different quarters of the principal town and among different tribes and villages, while several families were found to have more than one member with active secondary or tertiary lesions. All these features, together with the low cultural, economic, and sanitary habits of the population, would seem to indicate that the syphilis met in Asir should be included with the endemic treponematoses encountered elsewhere in the world.

Bantu Syphilis.—A report by Sachs and Selesnick [252] is based on a study of the treatment of syphilis in Bantu patients attending the Evaton Health Center during the past five years. An analysis of the results of treatment revealed certain discrepancies, namely, that inadequate arsenotherapy (less than 0.4

gm. of oxophenarside hydrochloride [Mapharside]) produced better results than were obtained with 6,000,000 units of pencillin procaine in oil with 2% aluminum monostearate. This anomaly was explained partly by the fact that if a final test is taken too early after the completion of treatment the results are of little value and are nearly always positive. A study of male Bantu admissions to Weskoppies Mental Hospital during 1952 was made by Lamont and Blignault,[253] to determine the reasons for certification. Among the 258 patients, 248 were given blood tests for syphilis, 61 of whom gave positive reactions. Of the 61, 14 had positive cerebrospinal fluid findings for general paralysis. Four cases were diagnosed as interstitial cerebral syphilis. Syphilis remains a major problem in the male Bantu. Roughly, 25% of all patients admitted had positive reactions for syphilis, and, of these, 20% had involvement of the central nervous system.

Venereal Diseases in the Belgian Congo.—The results of a survey presented to the Royal Academy of Medicine of Belgium [254] showed that the incidence of venereal diseases is increasing generally on an ascending curve, especially among the natives. The commonest is gonorrhea, which is twice or three times as frequent as syphilis. The epidemic index of syphilis among the white persons in the colony is higher than that which was reached at the time of the recent war and postwar epidemics.

Venereal Diseases Among Immigrants.—In the material of the outpatient clinic for skin and venereal diseases of the Hadassah Hospital, Tel Aviv, Berlin [255] encountered among the immigrants 17 instances of early syphilis, 40 of late symptomatic syphilis, a certain number of cases with a reliable history of the disease and about 500 cases of "latent" syphilis with various degrees of positive blood tests as the only indication of a syphilitic infection. These cases pose a troublesome problem. Berlin believes that there are many nonspecific positive reactions in the material studied.

Syphilis in Trinidad.—Sampath [256] reports that 2,246 pregnant Negro and East Indian women from San Fernando and the surrounding rural district were given qualitative Kahn tests for syphilis during the period June, 1951, to October, 1952. Of these, 131 (5.8%) had positive reactions. Markedly more syphilis was found in the city than in the country. Negroes showed three times as many positive reactions as the East Indians.

Latent Syphilis Ignorée and Syphilis Control During the Epidemic in Denmark, 1942 to 1949.—In an elaborate statistical analysis by Svendsen † of the results of serologic tests in the Statens Seruminstitut, the sole laboratory in Denmark where serologic tests are performed, Svendsen has demonstrated the epidemic of syphilis which occurred in Denmark beginning in 1942, reaching its climax in 1945 and subsiding thereafter. Latent syphilis, as well as early syphilis, increased sharply during this period. However, possibly as a result of the increase in the number of persons subjected to serologic tests for syphilis in Denmark, despite the recent epidemic the author believes that there are now fewer unrecognized cases of late syphilis in Denmark than there were in the past. He concludes that the control program in Denmark has been satisfactory from the point of view of finding the largest possible number of infected subjects as early as possible.

Syphilis Control in Turkey.—A report by Christiansen [258] on a six months' survey on the nature and extent of venereal disease in Turkey, with special reference to syphilis, has recently been published by WHO. The first part of the report summarizes the legislation relating to venereal diseases, outlines the present venereal disease control system, and includes descriptions of the work undertaken by public authorities, hospitals and dispensaries, mobile venereal disease control units, and laboratories throughout the country. Penicillin treatment was introduced in 1950, and treatment schedules, based on PAM, aqueous pencillin G procaine, and

† References 38 and 257.

crystalline penicillin G, were established by the Ministry of Health. The course of PAM treatment recommended for early syphilis consists of 1.2 mega units given weekly for 4 weeks, followed by five bismuth courses, 0.15 gm. bismuth usually being given weekly for 10 weeks, with an interval of four weeks between each course. The bismuth courses may, however, be shortened or prolonged in accordance with the stage of the disease, and the dose per injection may be modified according to the age of the patient. In the second part of the report the author enumerates certain recommendations for the reorientation, intensification, and expansion of the current control program. These recommendations are particularly concerned with the standardization and coordination of serodiagnostic facilities and services, the introduction of premarital serologic testing, and the establishment of case-finding and contact-tracing procedures. A proposed plan of operations for an eight-year period is also described.

It is of interest that some areas of endemic nonvenereal familial syphilis have been delimited also in Turkey, similar to those found in Yugoslavia, Saudi Arabia, India, and certain territories in Africa.

Investigation of Contacts Reported by Military Services—Massachusetts, 1952.—In a study of the results of investigation of contacts reported by the military services in Massachusetts in 1952, Fiumara [259] found that, in spite of the expansion of the armed services, the average age of the infected men and their contacts had not changed during the preceding four years. Prostitution accounted for only 6.3% of the infections. Taverns, bars, and restaurants were the focal point for most of the pick-ups, and home, hotel, and automobiles were most frequently named as places of exposure. A homosexual partner was named in less than 1% of the cases. Only 28% of the contact reports contained complete information. In these cases, 90% of the contacts were found and examined, whereas with incomplete information only 52% were located.

Decline and Fall of Syphilis in New York State.—Charting graphically and in tabular fashion the decline and fall of syphilis in New York State, DeMello and Vought [260] document the epidemic of syphilis which occurred between the years 1944 and 1947 and the subsequent sharp drop in the attack rate of syphilis, culminating in an all-time low in 1952. Morbidity rates for congenital syphilis showed a much smaller increase during the epidemic years, and morbidity rates for late syphilis have shown a steady decline since 1944. The rate of decline for the white and Negro races are almost identical, although the level for the Negro is very much higher than for the white. The authors conclude that the fact that late and congenital syphilis steadily declined during and after a major outbreak of syphilis is an encouraging sign that the disease is amenable to the control measures which have been in use. The parallel decline of early syphilis among the white and Negro population indicates that color or race, per se, interposes no barrier to syphilis control. The epidemic of syphilis during the late war years and immediately thereafter in an area where facilities for venereal disease control were reasonably adequate points to the conclusion that the control of syphilis involves more than antibiotic therapy. The authors predict that, despite our modern efficient therapeutic armamentarium, another outbreak of syphilis can occur under similar conditions but that our present methods of case-finding and therapy will minimize the impact of the outbreak and shorten its duration. They conclude that the ultimate of total control of syphilis is not yet at hand.

Venereal Disease Epidemiologic Study in Kansas City.—A brief report is presented by Byington and Wettig [261] on venereal disease contact interviewing and investigation in the Kansas City, Wyandotte County, area. In the first five months of 1953 a total of 28 cases of primary and secondary syphilis were reported. An epidemiologic chart, showing results of thorough contact interview and investigation among white teen-agers in Kansas City, Kan., from January through May, 1953, is given.

Venereal Disease Education, United States Navy.—Anderson [262] states that venereal disease education has two distinct goals: (1) motivating the individual person with the desire to avoid promiscuous extramarital sexual exposures and (2) educating the individual person concerning the venereal diseases, how they are contracted and the importance of early treatment, of contact investigation, and of prevention. Anderson briefly discusses the pamphlets, posters, motion picture films, and publications and other methods by which the Navy attempts to achieve these goals.

The Contemporary Defaulter in a Venereal Disease Clinic.—Horne,[263] in this second paper (see Horne, G. O.: *Brit. J. Ven. Dis.* **26:** 164, 1950), analyzes the findings of extended series of patients from the venereal disease clinic at Leeds (1950-1952). These patients included persons with early (primary, secondary, or early latent) syphilis, patients under observation after treatment for gonorrhea, and persons under observation after risk of contracting venereal disease. In each of the groups analyzed, the pattern of behavior with regard to default was identical with that of the corresponding groups reported in the earlier communication (Horne, 1950). The conclusions then drawn and their implications are confirmed by the present study: 1. In all these types of patient regular attendance is very rare after default has once occurred, and this default pattern is unaffected by personal or other influences. 2. There is little use in attempting to follow up patients who default while under observation after exposure to the risk of contracting venereal disease or after treatment for gonorrhea. 3. An assessment should be made of what constitutes a "defaulter" under contemporary conditions and more careful consideration given to the steps that should (or should not) be taken when default occurs. 4. Female patients receiving treatment for early syphilis behave in the same way as men. These results make an interesting contribution to the study of human behavior. The behavior of persons under treatment and observation for venereal diseases should be considered in planning the management of such patients, especially in view of the changing situation with regard to the venereal diseases and their treatment.

Clinical Report of the Rotunda Hospital: Nov. 1, 1951-Nov. 7, 1952.—During the year, 4,276 women were delivered in the Rotunda Hospital,[264] with 5 maternal deaths; 1,598 women were delivered in their own homes, with no maternal deaths, and 517 were operated on or required treatment in the gynecologic department, with 1 death. A detailed statistical report is presented of the services performed by the hospital in connection with these patients. Complications encountered, types of delivery, morbidity, and mortality are included. There were 36 cases of syphilis diagnosed in the antenatal period by means of the Wassermann and Kahn reactions, which are done routinely on every patient attending the antenatal department of the hospital. Treatment given was 5,400,000 units of penicillin G procaine. This treatment appears to protect the baby adequately in most cases; of 34 babies born alive only 4 had a positive Wassermann reaction after delivery. In 14 cases the x-ray appearances of the long bones suggested that syphilitic changes existed, however. In the whole series only two fetal lives were lost. All babies born of syphilitic mothers received a course of penicillin G procaine before discharge. There were also four other patients with syphilis delivered in the hospital. These patients were diagnosed and treated in general hospitals.

REFERENCES

1. Beerman, H.; Schamberg, I. L.; Nicholas, L., and Katzenstein, L.: Syphilis: A Review of the Literature, A.M.A. Arch. Int. Med. **93**:571-628 (April); 742-780 (May) 1954.

2. Dennie, C. C.: Syphilis—A Vanishing Disease, Mississippi Valley M. J. **75**:101-105 (July) 1953.

3. Sontheimer, M.: The Dread Comeback. Ladies Home J. **71**:38-39 (July) 1954.

4. Time **62**:71 (Dec. 21) 1953.

5. Venereal Disease Control Is Not Automatic, editorial, J.A.M.A. **155**:911-912 (July 3) 1954.

6. Lentz, J. W., and Beerman, H.: The Treatment of Venereal Diseases in Private Practice in Philadelphia, Am. J. Syph. **37**:427-438 (Sept.) 1953.

7. Moore, J. E.: The Changing Pattern of Syphilis 1941-1953, editorial, Ann. Int. Med. **39**:644-649 (Sept.) 1953.

8. Venereal Diseases, the Changing Problem, editorial, Brit. J. Ven. Dis. **29**:197 (Dec.) 1953.

9. Today's VD Control Problem: A Joint Statement to the Appropriation Committee of the Federal Congress, 1954, Amer. J. Syph. **38**:161-175 (May) 1954.

10. Wortmann, F.: Syphilis: Sammelreferat Juli 1952-Juni 1953, Dermatologica **107**:341-367, 1953.

11. Unknowns in Yaws, Brit. J. Ven. Dis. **29**:106-107 (June) 1953.

12. Venereal Infections and Treponematoses: Fourth Report of the WHO Expert Committee on Venereal Infections and Treponematoses, Geneva, World Health Organization, 1953.

13. Guthe, T., and Willcox, R. R.: Treponematoses, A World Problem, Geneva, World Health Organization, 1954.

14. Idsøe, O.; Guthe, T.; Christiansen, S.; Krag, P., and Cutler, J. C.: A Decade of Reorientation in the Treatment of Venereal Syphilis, Bull. World Health Organ. **10**:507-561, 1954.

15. Endemic Syphilis, Brit. J. Ven. Dis. **29**:108-109 (June) 1953.

16. Charpy, J., Editor: Le T.P.I. test de Nelson-Mayer: Troisième colloque de la Filiale marseillaise de la société française de dermatologie et de syphiligraphie, Paris, Masson & Cie., 1953.

17. Garcia, A.: Clinique et pathologie de la neurosyphilis, Paris, Masson & Cie., 1953.

18. Aron, H. C. S.: Paul Ehrlich: His Contributions to Medicine, J.A.M.A. **154**:969-972 (March 20) 1954.

19. Harrison, L. W.: Ehrlich Versus Syphilis, Brit. J. Ven. Dis. **30**:2-6 (March) 1954.

20. Marti-Ibanez, F.: The Mind and the World of Paul Ehrlich, 1854-1954, Internat. Rec. Med. **167**:143-154 (March) 1954.

21. Waksman, S. A.: Paul Ehrlich—as Man and Scientist, Internat. Rec. Med. **167**:136-142 (March) 1954.

22. Friedman, A. N.: Syphilis: Its Origin, Evolution and Therapy in Former Times, McGill M.J. **22**:153-160 (Oct.) 1953.

23. Hoffmann, E.: Einst and Jetzt: Syphilisbehandlung, München. med Wchnschr. **95**:669-671 (June 12) 1953.

24. Weiss, P., and Goldman, L.: Pre-Columbian Ceramic Vases of the Ancient Nazca Culture, Showing Possible Gummata of the Leg. Am. J. Syph. **38**:145-147 (March) 1954.

25. Turner, T. B.; Hollander, D. H., and Schaeffer, K.: Biological Investigations on Treponemes, Bull. World Health Organ. **8**:7-16, 1953.

26. Steinman, H. G.; Oyama, V. I., and Schulze, H. O.: The Nutritional Requirements of Treponemata: VI. The Total Vitamin Requirements of the Reiter Treponeme, J. Bact. **67**:597-602 (May) 1954.

27. Loeb, L.: Über den Nachweis der van Lennhoff bei zahlreichen Affektionen ungeklärter Ätiologie beschriebenen Spirochäten in histologischen Schnitten und die Frage der Wirksamkeit einer entsprechenden spirochätiziden Therapie, Dermatologica **107**:13-27, 1953.

28. Hård, S.: A Search For Treponemes in Mice with Experimental Syphilis, Acta dermat.-venereol. **33**:342-355, 1953.

29. Scott, V., and Dammin, G. J.: Morphologic and Histochemical Sequences in Syphilitic and in Tuberculous Orchitis in the Rabbit, Am. J. Syph. **38**:189-202 (May) 1954.

30. Probey, T. F.: Attempt to Produce a Penicillin-Resistant Strain of Treponema Pallidum in Experimental Syphilis, Am. J. Syph. **37**:369-373 (July) 1953.

31. Morton, H. E., and Ford, W. T.: Preliminary Observations of the Action of Penicillin on Treponema Pallidum in Vivo, Am. J. Syph. **37**:529-535 (Nov.) 1953.

32. Nell, E. E.: Comparative Sensitivity of Treponemes of Syphilis, Yaws and Bejel to Penicillin in Vitro, with Observations on Factors Affecting Its Treponemicidal Action, Am. J. Syph. **38**:92-106 (March) 1954.

33. Turner, T. B., and Schaeffer, K.: The Comparative Effect of Various Antibiotics in Experimental Syphilis, Am. J. Syph. **38**:81-91 (March) 1954.

34. Keller, R., and Morton, H. E.: Susceptibilities of Kazan, Nichols, and Reiter Strains of Treponema and Pleuropneumonia-like Organisms to the Antibiotic Erythromycin (Ilotycin), Am. J. Syph. **37**:379-382 (July) 1953.

35. Chacko, C. W.: A Study of the Treponema Immobilizing Antibody in Syphilis, Brit. J. Exper. Path. **34**:556-563 (Oct.) 1953.

36. Carpenter, C. M., and Boak, R. A.: An Evaluation of Commercial Prophylactics in Experimental Syphilis, Antibiotics & Chemother. **3**:415-417 (April) 1953.

37. Kolmer, J. A.: Penicillin by Oral Administration in the Prophylaxis and Abortive Treatment of Experimental Syphilis of Rabbits, Am. J. Syph. **38**:176-188 (May) 1954.

38. Danbolt, N.; Clark, E. G., and Gjestland, T.: The Oslo-Study of Untreated Syphilis: A Re-Study of the Boeck-Bruusgaard Material Concerning the Fate of Syphilitics Who Receive No Specific Treatment (A Preliminary Report), Acta dermat.-venereol. **34**:34-38, 1954.

39. Gaté, J.; Thivolet, J.; Simeray, A., and Rolland, M.: L'intradermo-réaction aux suspensions de tréponèmes pathogènes (souche Nichols) formolés: Son intèrèt et ses limites pour le diagnostic de l'infection syphilitique, Ann. méd. **54**:633-651, 1953.

40. Carney, R. G.: The Problem of Serologic Testing for Syphilis, J. Iowa M. Soc. **43**:377-380 (Sept.) 1953.

41. Reddy, D. J.: Some Problems in Syphilis, Indian J. Ven. Dis. **19**:58-62 (April-June) 1953.

42. Vogelsang, T. M.: Problems in the Seriodiagnosis of Syphilis, Tidsskr. norske lægfor. **74**: 292-300, 1954.

43. Dr. Hinton and the Wassermann Laboratory, Commonwealth **2**:19-23 (Jan.) 1954.

44. Standardization of Serologic Tests for Syphilis, Foreign Letters (Norway), J.A.M.A. **153**:663 (Oct. 17) 1953.

45. Mitra, A. K.; Biswas, S. K.; Sen, S., and Bhattacharjee, N. C.: Unitary *v.* Plural Conception of Antilipid Antibody in Syphilitic Serum, Brit. J. Ven. Dis. **29**:228-230 (Dec.) 1953.

46. Price, I. N. O.: An Investigation into the Use of Cardiolipin Antigens: II. Complement-Fixing Properties of Cardiolipin Wassermann Antigen, Brit. J. Ven. Dis. **29**:78-83 (June) 1953.

47. Price, I. N. O.: An Investigation into the Use of Cardiolipin Antigens: III. Choice of a Formula for Cardiolipin Wassermann Antigen for Use in the Whitechapel Wassermann Technique, Brit. J. Ven. Dis. **29**:175-178 (Sept.) 1953.

48. Schmidt, H.: Cardiolipin Antigen: III. An Examination of Specificity, Brit. J. Ven. Dis. **29**:84-94 (June) 1953.

49. Schmidt, H.: Cardiolipin Antigen: IV. Incidence of Positive Sero-Reactions for Syphilis in "Normal Persons," Acta dermat.-venereol. **34**:159-168, 1954.

50. Bossak, H. N.; Harris, A.; Duncan, W. P.; Olansky, S., and Chester, B. J.: The Mazzini Cardiolipin Microflocculation Test in the Serology of Syphilis, Am. J. Syph. **37**:536-539 (Nov.) 1953.

51. Kahn, R. L., and McDermott, E. B.: Specificity Results of Kahn and Cardiolipin Tests in Recent Official Evaluations, Univ. Michigan M. Bull. **19**:163-168 (July) 1953.

52. Tonks, D. B., and Allen, R. H.: The Use of Some Synthetic Phosphatides in Antigens for the Serodiagnosis of Syphilis, Science **118**:55-56 (July 10) 1953.

53. Mountford, D.: The Quantitative Complement Fixation Test with Special Reference to Low-Titered Sera, Australian J. Exper. Biol. & M. Sc. **31**:105-119 (April) 1953.

54. Cannefax, G. R.: Observations on the Optimal Zone Reaction and Seroresistance, Am. J. Syph. **37**:344-347 (July) 1953.

55. Cannefax, G. R.; Beyer, H. R., and Johnwick, E. B.: A Study of the Effects of Certain Temperatures and Time Limits on the VDRL Slide Test, Am. J. Syph. **37**:348-354 (July) 1953.

56. Kahn, R. L.: Clarification of Syphilitic and Nonsyphilitic Serodiagnostic Reactions, J.A.M.A. **152**:1204-1207 (July 25) 1953.

57. Herzog, H., and Pulver, W.: Die pseudoluische (Wassermann-positive) Viruspneumonie: Erfahrungeran 37 Fällen der Jahre 1940 bis 1952, Schweiz. med. Wchnschr. **83**:227-234, 1953.

58. Cutler, J. C.; Chester, B. J., and Price, E. V.: Studies on the Comparative Behavior of Various Serologic Tests for Syphilis: III. A Report on Return to Seronegativity Following Successfully Treated Primary and Secondary Syphilis (with Remarks on the Serologic Response of Chronic Biologic False Positive Reactors Subsequently Infected with Syphilis), Am. J. Syph. **37**:514-528 (Nov.) 1953.

59. Djanian, A. Y.: V.D.R.L. Tube Test: A Comparison with the Kahn and Kolmer Tests for Syphilis, Brit. J. Ven. Dis. **29**:238-239 (Dec.) 1953.

60. McLeod, C. P., and Magnuson, H. J.: Agglutination of Treponema Pallidum in Syphilitic Serums, Pub. Health Rep. **68**:747-755 (Aug.) 1953.

61. Nelson, A., Jr.: The Immune-Adherence Phenomenon: An Immunologically Specific Reaction between Microorganisms and Erythrocytes Leading to Enhanced Phagocytosis, Science **118**:733-737 (Dec. 18) 1953.

62. Olansky, S.; Harris, A., and Casey, H.: Immune-Adherence Test for Syphilis, Pub. Health Rep. **69**:521-526 (June) 1954.

63. Meinicke, K.: Brief aus Marseille: Colloquium über den Treponema pallidum-Immobilisierungstest von Nelson und Mayer, Hautarzt **4**:231-232 (May) 1953.

64. Beerman, H.: The Treponemal Immobilization Test, Am. J. M. Sc. **226**:425-441 (Oct.) 1953.

65. Miller, J. L.; Slatkin, M. H.; Brodey, M.; Wechsler, H. L., and Hill, J. H.: Studies with the Treponemal Immobilizing Test, J.A.M.A. **154**:1241-1247 (April 10) 1954.

66. Miller, G. W., and Smith, H. B.: Use of the Treponema Pallidum Immobilization Test in a Syphilis Control Program, Am. J. Syph. **37**:424-426 (Sept.) 1953.

67. Bureau, Y.; Jarry, and Barrière: Que vaut le test de Nelson dans les syphilis nerveuses? Bull. Soc. franç. dermat. et syph. **60**:203-204 (March-April) 1953.

68. Recent Progress with the Treponemal Immobilization Test, Brit. J. Ven. Dis. **29**:240-242 (Dec.) 1953.

69. Nielsen, H. A.: Clinical Value of the T.P.I. Test, Acta dermat.-venereol. **34**:102-109, 1954.

70. Thivolet, J.; Rolland, M., and Chardonnet: Étude des facteurs intervenant dans la réaction du test d'immobilisation de Nelson-Mayer, Ann. biol. clin. **11**:332-338 (May-June) 1953.

71. Doepfmer, R.; Greifelt, A., and Gregorczyk, K.: Die Bedeutung des Nelson-Tests im Rahmen der modernen Lues-Serologie (mit eigenen Erfahrungen an 450 Nelson-Tests), Ztschr. Hyg. **138**:427-441, 1954.

72. Doepfmer, R.; Gregorczyk, K., and Greifelt, A.: Die klinische Bedeutung des Nelson-Tests für die Diagnose der Lues, Med. Wchnschr. **48**:1398-1401 (Sept. 18) 1953.

73. Ranque, J., and Moignoux, J. B.: Saturation des anticorps immobilisants de Nelson par des tréponèmes tués (T. pallidum, souche Nichols), Comp. rend. Soc. biol. **146**:1762-1763 (Nov.) 1952.

74. Benazet; Vigne; Thivolet, J., and Rolland, R.: Intérêt du test d'immobilisation des tréponèmes de Nelson (TIT) pour affirmer la syphilis sérologique chez un paludéen à sérologie classique oscillante, Bull. Soc. franç. dermat. et syph. **60**:192-194 (March-April) 1953.

75. Ranque, J., and Tramier, G.: Étude statistique comparative des réponses fournies que le test de Nelson et les methodes serologiques, Bull. Soc. franç. dermat. et syph. **60**:376-378 (July-Oct.) 1953.

76. Michel, P. J., and Saint-Paul, J.: Réflexions à propos d'une quinzane de tests de Nelson, Bull. Soc. franç. dermat. et syph. **60**:194-195 (March-April) 1953.

77. Jaeger, M., and Delancretaz, J.: Importance du test d'immobilisation des tréponèmes (de Nelson) dans le séro-diagnostic de la syphilis a ses différents stades, Dermatologica **106**:256-264, 1953.

78. Benazet; Vigne; Thivolet, J., and Rolland, R.: Intérêt du test d'immobilisation des tréponèmes de Nelson (T.I.T.) pour affirmer la syphilis serologique chez un paludéen à serologie classique oscilante, Lyon méd. **188**:408-410 (May 24) 1953.

79. Wheeler, A. H.: The Treponema Pallida Immobilization Test in the Diagnosis of Syphilis, J. Michigan M. Soc. **52**:859-864 (Aug.) 1953.

80. Fried, S.: Significance of Positive Serologic Tests, M. Bull. U.S. Army Europe **10**:159-162 (July) 1953.

81. Olivier, Benazet, Thivolet, Rolland: Le test d'immobilisation des tréponèmes de Nelson; ses applications, son intérêt pratique dans l'armée, Rev. corps san. mil. **9**:317-341 (Sept.) 1953.

82. Rainaut: Intérêt de l'utilisation précoce du T.I.T. en cas de négativité de la réaction de Bordet-Wassermann, Bull. Soc. franç. dermat. et syph. **60**:384-385 (July-Oct.) 1953.

83. Harrell, E. R.: A Comparison of Results Obtained by the Treponema Pallidum Immobilization Test and the Kahn Verification Test, Am. J. Syph. **37**:330-337 (July) 1953.

84. Roy, A. M.; Hill, J. H.; Gowdey, J. L.; Kelcec, L. C., and Rein, C. R.: A Comparison of the Neurath and Treponema Pallidum Immobilization Procedures, Am. J. Syph. **37**:338-343 (July) 1953.

85. Delacretaz, J.: Technique du test d'immobilisation des tréponèmes pales, Dermatologica **106**: 264-265, 1953.

86. Meinicke, K.: Technik des Treponema Pallidum-Immobilisierungs-Tests (T.P.I.-Nelson-Test), Hautarzt **4**:268-272 (June) 1953.

87. Greifelt, A.; Gregorczyk, K., and Doepfmer, R.: Zur Technik des Nelson-Tests und desen neuesen Modifikiationen, Arch. Dermat. u. Syph. **197**:105-118, 1954.

88. Nielsen, H. A.: Elimination of Inconclusive Results in the Treponemal Immobilization Test, Nature, London **171**:1030 (June 6) 1953.

89. Portnoy, J. P.; Olansky, S., and Edmundson, W. F.: Studies of the Treponema Pallidum Immobilization (TPI) Test: III. Studies on Reproducibility, Effect of Treponemal Concentration, and Failure to Demonstrate Sensitization in Vivo, Am. J. Syph. **37**:413-423 (Sept.) 1953.

90. Kolmer, J. A., and Lynch, E. R.: False Positive Reactions in the Serologic Diagnosis of Syphilis, Am. J. Clin. Path. **23**:854-865 (Sept.) 1953.

91. Nelson, R. A. J., and Kolmer, J. A.: Treponemal Immobilization Tests, Am. J. Clin. Path. **24**:207-208 (Feb.) 1954.

92. Roemer, G. B., and Schlipköter, H. W.: Die Spirochätenagglutination, eine einfache Reaktion zur Lues-Diagnostik im Liquor, Deutsch med. Wchnschr. **78**:345-347 (March 6) 1953.

93. Flodén, C. H.: Protein "Patterns" of Cerebro-Spinal Fluid in Different Stages of Syphilis Before and After Therapy, Acta dermat.-venereol. **34**:43-46, 1954.

94. Cutler, M., and Cutler, P.: Iatrogenic Meningitis, New Jersey M. Soc. J. **50**:510-514 (Nov.) 1953.

95. Fatal Syphilis, editorial, Brit. J. Ven. Dis. **29**:57 (June) 1953.

96. McElligott, G. L. C.: Fatal Syphilis, Brit. J. Ven. Dis. **29**:58-63 (June) 1953.

97. Ross, A. O. F.: Fatal Syphilis: A Review of Certification in Liverpool, 1938-1943, Brit. J. Ven. Dis. **29**:64-66 (June) 1953.

98. Newcomb, W. D.: Fatal Syphilis, Brit. J. Ven. Dis. **29**:67-70 (June) 1953.

99. Laymon, C. W.; Balogh, C., and Dixon, A.: Chancriform Pyoderma, Am. J. Syph. **38**:57-62 (Jan.) 1954.

100. Kallos, A.: Infectious Mononucleosis with Penile Ulceration, A. M. A. Arch. Dermat. & Syph. **69**:618-619 (May) 1954.

101. Rees, E.: Acquired Syphilis in Children: Report of 6 Cases, Brit. J. Ven. Dis. **30**:19-23 (March) 1954.

102. Syphilis in Would-Be Blood Donors, Foreign Letters (Sweden), J. A. M. A. **152**:1361-1362 (Aug. 1) 1953.

103. Whitaker, H. T., and Moore, R. M.: Gumma of the Breast, Surg., Gynec. & Obst. **98**:473-477 (March) 1954.

104. Leather, H. M.: Syphilitic Mediastinitis, Lancet **2**:116-118 (July 18) 1953.

105. Lawlor, M. K., and Roden, K. S.: Tertiary Syphilis of the Uterus and Adnexa, J. Obst. & Gynec. Brit. Emp. **60**:502-507 (Aug.) 1953.

106. Røjel, J.: The Interrelation Between Uterine Cancer and Syphilis: A Patho-Demographic Study, Acta. path. et microbiol. scandinav., Supp. 97, pp. 1-82, 1953.

107. Robinson, W. D.; Boland, E. W.; Bunim, J. J.; Crain, D. C.; Engleman, E. B.; Graham, W.; Lockie, L. M.; Montgomery, M. M.; Ragan, C.; Ropes, M. W.; Rosenberg, E. F., and Smyth, C. J.: Rheumatism and Arthritis: Review of American and English Literature of Recent Years (Tenth Rheumatism Review), Ann. Int. Med. **39**:498-618 (Sept.); 757-906 (Oct.) 1953.

108. Putkonen, T.; Teir, H., and Pyörälä, K.: Syphilitic Juxta-Articular Nodes, Brit. J. Ven. Dis. **29**:71-77 (June) 1953.

109. Sheppe, W. M.: Neuropathic (Charcot's) Joints Occurring in Diabetes Mellitus, Ann. Int. Med. **39**:625-630 (Sept.) 1953.

110. Engeset, A.; Eek, S., and Gilje, O.: On the Significance of Growth in Roentgenological Skeletal Changes in Early Congenital Syphilis, Am. J. Roentgenol. **69**:542-556 (April) 1953.

111. Peralta, A.: Penicilinoterrapía de la sífilis cardiovascular: Observaciones clínicas inmediatas y a largo plazo resultados que se basan en estudios histopatológicas, Thesis, Universidad Nacional Mayor de San Marcos Facultad de Medicina, Lima, Peru, 1953.

112. Hutcheson, J. M., Jr.; Hejtmancik, M. R., and Herrmann, G. R.: Changes in the Incidence and Types of Heart Disease: A Quarter-Century Follow-Up in a Southern Clinic and Hospital, Am. Heart J. **46**:565-575 (Oct.) 1953.

113. Webster, B.; Rich, C., Jr.; Densen, P.; Moore, J. E.; Nicol, C. S., and Paget, P.: Studies in Cardiovascular Syphilis: III. The Natural History of Syphilitic Aortic Insufficiency, Am. J. Syph. **37**:301-329 (July) 1953; Am. Heart J. **46**:117-145 (July) 1953.

114. Gay, B. B., Jr., and Walker, J. F.: Aneurysm of the Innominate Artery: Review of Clinical and Radiologic Findings in 18 Cases, Radiology **60**: 804-813 (June) 1953.

115. Renner, W. F., and Sindelar, J.: Rupture of a Thoracic Aneurysm into the Stomach, J. A. M. A. **153**:102-103 (Sept. 12) 1953.

116. Calenda, D. G., and Uricchio, J. F.: Gastrointestinal Hemorrhage Due to Rupture of Aortic Aneurysm into the Esophagus, J. A. M. A. **153**: 548-549 (Oct. 10) 1953.

117. Baer, S.: Rupture of Aortic Aneurysm into Esophagus, Correspondence, J. A. M. A. **153**:1571 (Dec. 26) 1953.

118. Jackson, A., and Slavin, M.: Dissecting Aneurysm of the Aorta: Report of 6 Cases with Etiopathologic and Diagnostic Considerations, Angiology **4**:357-373 (Aug.) 1953.

119. England, D. L.: Rupture of Aortic Aneurysm into Superior Vena Cava, A. M. A. Arch. Int. Med. **92**:897-905 (Dec.) 1953.

120. Jennings, G. H.: Rupture of an Aortic Aneurysm into the Pulmonary Artery, Brit. Heart J. **15**:456-458 (Oct.) 1953.

121. Ross, R. S., and McKusick, V. A.: Aortic Arch Syndromes: Diminished or Absent Pulses in Arteries Arising from Arch of Aorta, A. M. A. Arch. Int. Med. **92**:701-740 (Nov.) 1953.

122. Vernon, S., and Davis, W. H.: Neurosyphilis Precipitated by Trauma: A Case Report, Connecticut M. J. **18**:124-125 (Feb.) 1954.

123. Malzberg, B.: Mental Disease Among Negroes in New York State, 1939-1941, Ment. Hyg. **37**:450-476 (July) 1953.

124. Goldblatt, S.: Studies in Pallesthesia: Quantitative Vibratory Levels in Syphilis and in Lymphogranuloma Venereum, Am. J. Syph. **37**:471-485 (Sept.) 1953.

125. Okinaka, S.; Murata, T.; Nishikawa, M.; Ikeda, M.; Kuroiwa, Y., and Shizume, K.: A Contribution to Pathogenesis of the Gastric Crisis: A Case Report of the Spinal Syphilis Which Showed Painful Abdominal Girdle Sensation and Peristaltic Unrest of Stomach and Intestine, Folia psychiat. et neur. jap. **5**:127-134 (Dec.) 1951.

126. Doyle, J. O., and Campbell, D. J.: Masked Perforation of a Gastric Ulcer in a Case of Tabes Dorsalis, Brit. J. Ven. Dis. **29**:164-165 (Sept.) 1953.

127. Patrick, S. I., and Reeves, R. J.: Observations of Gastric Motility During Gastric Crisis, A. M. A. Arch. Int. Med. **92**:920-925 (Dec.) 1953.

128. Holland, H. W.: Tabetic Spinal Arthropathy, Proc. Roy. Soc. Med. **46**:747-752 (Sept.) 1953.

129. Neill, K. G.: An Unusual Case of Syphilitic Parkinsonism, Brit. M. J. **2**:320-322 (Aug. 8) 1953.

130. Cause of Blindness in England, Foreign Letters (England), J. A. M. A. **153**:1469-1470 (Dec. 19) 1953.

131. Berens, C., and Bickerton, J. H.: Uveitis and Blindness, Sight-Saving Rev. **23**:198-207 (Winter) 1953.

132. Jaffe, N. S.: Pupil in Syphilis, Am. J. Ophth. **36**:493, 1953.

133. Pines, N.: A reversibilidade do sinal pupilar de Argyll Robertson na tabes, J. méd., Pôrto **20**: 105, 1952.

134. Thiébaut, F., and Helle, J.: Signe d'Argyll Robertson unilateral, Rev. oto-neuro-oftal. **25**:321, 1953.

135. Sprofkin, B. E.: Adie's Syndrome and the Adler-Scheie Mecholyl Test, Neurology **3**:910-915 (Dec.) 1953.

136. Gross, B. A., and Meyer, G. P.: Ocular Examination in Diagnosis of Congenital Syphilis, Am. J. Syph. **38**:30-43 (Jan.) 1954.

137. Cook, C., and Langham, M.: Corneal Thickness in Interstitial Keratitis, Brit. J. Ophth. **37**:301-304 (May) 1953.

138. Stevens, H.: Cogan's Syndrome, Nonsyphilitic Interstitial Keratitis with Deafness, A.M.A. Arch. Neurol. & Psychiat. **71**:337-343 (March) 1954.

139. Prevention of Congenital Syphilis, Brit. J. Ven. Dis. **302**:49-52 (March) 1954.

140. Tests for Syphilis in Pregnant Women, Foreign Letters (Norway), J. A. M. A. **153**:875-876 (Oct. 31) 1953.

141. Berlin, C., and Meyrovitz, C.: Syphilis in Pregnancy, Brit. J. Ven. Dis. **30**:28-30 (March) 1954.

142. MacFarlane, W. V.: Familial Investigation in Syphilis, Brit. J. Ven. Dis. **29**:203-209 (Dec.) 1953.

143. Wright, S. W., and Wright, P. M.: A Study of the Incidence of Congenital Syphilis Among Living Infants in Nagasaki, Japan, Am. J. Syph. **38**:1-6 (Jan.) 1954.

144. Mitchell, H. S.: Congenital Syphilis of the Stomach, Ann. Int. Med. **40**:369-374 (Feb.) 1954.

145. Edmondson, P. W.: Congenital Syphilis of the Lungs, Brit. M. J. **1**:1148-1149 (May 23) 1953.

146. Bowie, F. J. T., and Simpson, R. G.: Cardio-Aortic Involvement in Congenital Syphilis with Co-Existent Rheumatic Heart Disease, Brit. Heart J. **15**:264-266 (April) 1953.

147. Rosenblum, R., and Cetnar, E. J.: Paroxysmal Cold Hemoglobinuria in Treated Congenital Syphilis, A. M. A. Arch. Int. Med. **93**:304-306 (Feb.) 1954.

148. Caver, C. V.: Third Generation Syphilis, Hawaii M. J. **12**:448-449 (July-Aug.) 1953.

149. Bonugli, F. S.: Third-Generation Syphilis and Bilateral Interstitial Keratitis Occurring in All the Surviving Members of 2 Generations, Brit. J. Ven. Dis. **30**:24-27, 1954.

150. Danbolt, N.: Syfilis-Bekjempelsen, Tidsskr. norske lægefor. **79**:304-305, 1954.

151. Thomas, E. W.: Problems in the Diagnosis and Treatment of Syphilis, J. Michigan M. Soc. **52**:854-858 (Aug.) 1953.

152. Idsøe, O., and Guthe, T.: Penicillin Treatment of Treponemal Disease, with Special Reference to PAM Therapy in Syphilis, Tidsskr. norske lægefor. **74**:275-290 (April 15) 1954.

153. Willcox, R. R.: Treatment Before Diagnosis in Venereology, Brit. J. Ven. Dis. **30**:7-13 (March) 1954.

153a. King, A.: For and Against Treatment Before Diagnosis, Brit. J. Ven. Dis. **30**:13-18 (March) 1954.

154. Willcox, R. R.: A Study of Current Treatment Practices in Early Syphilis Throughout the World, Bull. World Health Organ. **10**:579-617, 1954.

155. Smith, C. A.; O'Brien, J. F.; Simpson, W. G.; Harb, F. W., and Shafer, J. K.: Treatment of Early Infectious Syphilis with N,N'Dibenzylethylenediamine Dipenicillin G, Am. J. Syph. **38**:136-142 (March) 1954.

156. Shafer, J. K., and Smith, C. A.: Treatment of Early Infectious Syphilis with N,N'Dibenzylethylenediamine Dipenicillin G, Bull. World Health Organ. **10**:619-626, 1954.

157. Guthe, T., and Danbolt, N.: Simplification of Penicillin Treatment in Syphilis: Preliminary Results with Benzylamine Penicillin Salts, Tidsskr. norske lægefor. **74**:290-292, 1954.

158. de Graciansky, P., and Grupper, C.: Résultats et commentaires d'une expérience de traitement pénicilliné rapide de la syphilis récente, Semaine hôp. Paris **29**:2889-2904 (Oct. 2) 1953.

159. Feldreich, H.: Penicillin Treatment of Early Syphilis at St. Goran's Hospital, Acta dermat.-venereol. **34**:39-42, 1954.

160. Rein, C. R.; Buckwalter, F. H.; Mann, C. H.; Landy, S. E., and Flax, S.: Time-Dosage Relationship in the Treatment of Treponemal Diseases with a New Combination of 3 Penicillin Salts: Laboratory and Clinical Basis for Effective Therapy, J. Invest. Dermat. **21**:435-446 (Dec.) 1953.

161. Thomas, E. W.; Rein, C. R.; Landy, S. E., and Kitchen, D. K.: Results of Treatment of Early Syphilis with a Single Injection of Procaine Penicillin G in Oil and Aluminum Monostearate, Am. J. Syph. **37**:374-376 (July) 1953.

162. Shafer, J. K.; Usilton, L. J., and Price, E. V.: Long-Term Studies of Results of Penicillin Therapy in Early Syphilis, Bull. World Health Organ. **10**:563-578, 1954.

163. Danbolt, N., and Berdal, T.: Follow-Up Examinations of Early Syphilis Treated with Penicillin-Arsenoxide-Bismuth with Observation Time of up to 5 Years, Acta dermat.-venereol. **33**:412-420, 1953.

164. Thomas, E. W., and Gleesen, G. A.: A Long-Term Evaluation of the Efficacy of Mapharsen and Typhoid Vaccine, Including a Comparison with Penicillin, in the Treatment of Early Syphilis, Am. J. Syph. **37**:458-465 (Sept.) 1953.

165. Perdrup, A.; Heilesen, B., and Sylvest, B.: Follow-Up Examination of 157 Patients with Early Mucocutaneous Syphilis Treated with Penicillin and Followed for 1 to 4 Years, Acta dermat.-venereol. **34**:133-135, 1954.

166. Lee, S. S.: Reevaluation of Previously Treated Syphilis Cases, West Virginia M. J. **49**:99-100 (April) 1953.

167. Barnett, C. W.; Epstein, N. N.; Brewer, A. F.; Koch, R. A., and Beirne, G. A.: Effect of Treatment in Late Latent Syphilis, A. M. A. Arch. Dermat. & Syph. **69**:91-99 (Jan.) 1954.

168. Chester, B. J.; Cutler, J. C., and Price, E. V.: Serologic Observations Following Penicillin Treatment for Latent Syphilis, Am. J. Syph. **38**:7-17 (Jan.) 1954.

169. Cannefax, G. R., and Johnwick, E. B.: The Observation of Serologic Response Following Re-Treatment for Seroresistance and Theoretical Considerations on the Meaning of Seroresistance, Am. J. Syph. **38**:18-23 (Jan.) 1954.

170. Eisenberg, H., and Brandfonbrener, M.: Observations on Penicillin-Treatment of Cardiovascular Syphilis: I. Uncomplicated Aortitis, Am. J. Syph. **37**:439-441 (Sept.) 1953.

171. Eisenberg, H., and Brandfonbrener, M.: Observations on the Penicillin Treatment of Cardiovascular Syphilis: II. Complicated Aortitis, Am. J. Syph. **37**:442-448 (Sept.) 1953.

172. Sinclaire, H. A., and Webster, B.: The Effect of Penicillin Treatment on the Microscopic Appearance of Syphilitic Aortitis, Am. J. Syph. **38**:54-56 (Jan.) 1954.

173. Texier, L., and Régnier: Traitement de la syphilis cardio-aortique par la pénicilline: Historique et technique, Semaine hôp. Paris **30**:1422-1424 (April 2) 1954.

174. Johnston, J. B.; Kirklin, J. W., and Brandenburg, R. O.: The Treatment of Saccular Aneurysms of the Thoracic Aorta, Proc. Staff Meet., Mayo Clin. **28**:723-728 (Dec. 16) 1953.

175. Penick, R. M.: Treatment of Aneurysms of the Great Vessels by Wiring, S. Clin. North America **33**:1049-1055 (Aug.) 1953.

176. de Bakey, M. D., and Cooley, D. A.: Excisional Therapy of Aortic Aneurysms, Am. Surgeon **19**:603-612 (July) 1953.

177. Cooley, D. A., and deBakey, M. E.: Surgical Considerations of Excisional Therapy for Aortic Aneurysms, Surgery **34**:1005 (Dec.) 1953.

178. Bahnson, H. T.: Considerations in the Excision of Aortic Aneurysms, Ann. Surg. **138**:377-386 (Sept.) 1953.

179. Prognosis in General Paresis, Foreign Letters (England), J. A. M. A. **154**:1297 (April 10) 1954.

180. Dammann, H. J., and Schmidt, E.: Zur Behandlung der Neuro-Lues mit Penicillin, Deutsche med. Wchnschr. **78**:1231-1233 (Sept. 4) 1953.

181. Verjall, A.: Neurosyphilis, Nederl. tijdschr. eneesk. **97**:1767 (July 4) 1953.

182. Cohn, W. S.: Observations on 36 Patients with General Paresis Treated with Penicillin-Malaria and Penicillin Alone, Psychiat. Quart. **27**:637-649 (Oct.) 1953.

183. Petersen, M. C.: Electrotonic Treatment in Dementia Paralytica, J. Nerv. & Ment. Dis. **118**: 162-167 (Aug.) 1953.

184. Lees, R.: Surgical Aspects of Tabes Dorsalis, Brit. J. Ven. Dis. **29**:198-202 (Dec.) 1953.

185. Thomas, E. W.: Blood and Spinal Fluid Tests for Reagin after Treatment of Neurosyphilis, J. A. M. A. **153**:718-722 (Oct. 24) 1953.

186. Kenney, J. A., Jr., and Curtis, A. C.: Treatment of Syphilitic Optic Atrophy by Penicillin, With and Without Therapeutic Malaria, Am. J. Syph. **37**:449-457 (Sept.) 1953.

187. Oksala, A.: Some Observations on the Treatment of Interstitial Keratitis with Penicillin, Malaria, and Cortone, Am. J. Syph. **37**:540-544 (Nov.) 1953.

188. Klauder, J. V., and Meyer, G. P.: Corticotropin, Thyroid, Testosterone in Syphilitic Interstitial Keratitis, A. M. A. Arch. Ophth. **51**:432-444 (April) 1954.

189. Keen, P.: Potassium Iodide in the Treatment of Syphilis, Brit. J. Ven. Dis. **29**:168-174 (Sept.) 1953.

190. Hosoya, S.; Soeda, M.; Komatsu, N.; Okada, K., and Watanabe, S.: Studies on Trichomycin: II. Antibiotic Activities Against Trichomonas, Candida, and Treponema Pallidum, J. Antibiotics, Ser. A, Tokyo **6**:92-97 (April) 1953.

191. Dunlop, E. M., and Robinson, R. C. V.: Intravenous Terramycin in the Treatment of Early Syphilis and Granuloma Inguinale, Am. J. Syph. **38**:24-29 (Jan.) 1954.

192. Alexander, L. J., and Schoch, A. G.: Erythromycin in Venereal Diseases, Am. J. Syph. **38**:107-109 (March) 1954.

193. Kern, R. A., and Wimberley, N. A., Jr.: Penicillin Reactions: Their Nature, Growing Importance, Recognition, Management and Prevention, Am. J. M. Sc. **266**:357-375 (Oct.) 1953.

194. Grekin, R. H., and O'Brien, J. F.: Anaphylactic Reactions from Bicillin, Am. J. Syph. **38**:143-144 (March) 1954.

195. Sterling, A.: Anaphylactic Shock Following Penicillin Therapy in Bronchial Asthma, J. Allergy **24**:542 (Nov.) 1953.

196. Pick, J. F., and Patterson, J. F.: Fatal Anaphylactic Shock Due to Penicillin, Brit. M. J. **2**: 605 (Sept. 12) 1953.

197. Bell, R. C.: Sudden Death Following Injection of Procaine Penicillin, Lancet **1**:13-17 (Jan.) 1954.

198. Fein, B. T.: Anaphylactoid Reaction to the Hydriodide of Diethylaminoethyl Ester of Penicillin G (Neo-Penil): Report of a Case, New England J. Med. **249**:368-369 (Aug. 27) 1953.

199. Greenfield, H. B.: Anaphylaxis to Intramuscular Injection of Penicillin in Oil, New England J. Med. **249**:258 (Aug. 6) 1953.

200. Welch, H.; Lewis, C. N.; Kerlan, I., and Putnam, L. E.: Acute Anaphylactoid Reactions Attributable to Penicillin, Antibiotics **3**:891-895 (Sept.) 1953.

201. Sohval, A. R.: Severe Immediate Constitutional Reaction to Penicillin, J. A. M. A. **152**: 1430-1431 (Aug. 8) 1953.

202. Fairlie, C. W., and Kendall, R. E.: Fatal Staphylococcus Enteritis Following Penicillin and Streptomycin Therapy, J. A. M. A. **153**:90-94 (Sept. 12) 1953.

203. Katzenellenbogen, I.: Side-Effects of Penicillin, Foreign Letters (Israel), J. A. M. A. **154**: 1022 (March 20) 1954.

204. Jennings, P. B., and Olansky, S.: The Use of Procaine Amide in the Treatment and Prevention of Penicillin Reaction, Ann. Int. Med. **40**: 711-720 (April) 1954.

205. Alexander, L. J.: Desensitization of the Penicillin-Sensitive Patient, A. M. A. Arch. Dermat. & Syph. **68**:323-327 (Sept.) 1953.

206. Brodey, M., and Nelson, C. T.: Use of Cortisone During Penicillin Treatment of Secondary Mucocutaneous Syphilis in a Hypersensitive Patient, New England J. Med. **250**:1069-1071 (June 24) 1954.

207. Osgood, E. E.: Drug Induced Hypoplastic Anemias and Related Syndromes, Ann. Int. Med. **39**:1173-1188 (Dec.) 1953.

208. Snivley, G. G.; Hattersley, P. G., and Nolan, L. E.: Aplastic Anemia Following Corticotropin Therapy, J. A. M. A. **152**:1223-1224 (July 25) 1953.

209. Edmunds, A. W. B.: Aplastic Anaemia and Severe Hepatic Zonal Necrosis After Anti-Syphilitic Treatment, Brit. J. Ven. Dis. **30**:45-48 (March) 1954.

210. Pocock, D. G.: Re-Evaluation of the Etiology of Postarsphenamine Jaundice, Am. J. M. Sc. **227**:21-31 (Jan.) 1954.

211. Willcox, R. R.: The Treponematoses, Glasgow M. J. **34**:281-298 (July) 1953.

212. Monnerot-Dumaine, M.: Tréponèmatoses exotiques, Presse méd. **61**:351-352 (March) 1953.

213. Poindexter, H. A.: An Analytical Study of 45,000 Consecutive Admissions to a Clinic in Monrovia, Liberia, West Africa, J. Nat. M. A. **45**:345-349 (Sept.) 1953.

214. Bonne, W. M.; Guthe, T., and Reynolds, F. W.: The Role of the World Health Organization in Yaws Control, Bull. World Health Organ. **8**:371-377, 1953.

215. Keeny, S. M.: The Role of the United Nations International Children's Emergency Fund in Yaws Control, Bull. World Health Organ. **8**:379-390, 1953.

216. Hill, K. R.: Non-Specific Factors in the Epidemiology of Yaws, Bull. World. Health Organ. **8**:17-47, 1953.

217. Rein, C. R.: Diagnostic Aids in Mass-Treatment Campaigns against Yaws, Bull. World Health Organ. **8**:245-254, 1953.

218. Hackett, C. J.: The Principles and Practice of Yaws Control, Brit. M. J. **2**:74-76 (July 11) 1953.

219. Guimaraes, F. N.: Yaws in Brazil, Bull. World Health Organ. **8**:225-237, 1953.

220. Jungalwalla, N.: Planning for Yaws Control in South-East Asia, Bull. World Health Organ. **8**:213-223, 1953.

221. Hackett, C. J.: Extent and Nature of the Yaws Problem in Africa, Bull. World Health Organ. **8**:129-182, 1953.

222. Willcox, R. R.: Marginal Interests of Yaws Campaigns in Africa, Am. J. Syph. **38**:44-47 (Jan.) 1954.

223. Yaws-Control Programme In India Expanded, Chron. World Health Organ. **7**:266-267 (Sept.) 1953.

224. Soetopo, M., and Wasito, R.: Experience with Yaws Control in Indonesia: Preliminary Results with a Simplified Approach, Bull. World Health Organ. **8**:273-291, 1953.

225. Sepulveda, G., Jr., and Ibarra, L. M.: The Effectiveness of Penicillin in the Treatment of Yaws (Primary and Secondary): Preliminary report, J. Philippine M. A. **29**:727-733 (Dec.) 1953.

226. Kitchen, D. K., and Rein, C. R.: Time-Dosage Relation in Penicillin Therapy with Special Reference to Yaws: I. Laboratory Basis for Effective Therapy, Bull. World Health Organ. **8**:77-89, 1953.

227. Rein, C. R., and Kitchen, D. K.: Time-Dosage Relation in Penicillin Therapy, with Special Reference to Yaws: II. Clinical Basis for Effective Therapy, Bull. World Health Organ. **8**:91-106, 1953.

228. Grin, E. K.; Guthe, T.; La-ong Payanandha; D'Mello, J. M. F., and Swaroop, A. S.: The Treatment of Yaws with Benzathine Penicillin G, Am. J. Syph. **38**:397-404 (Sept.) 1954.

229. Levitan, S.; Rodriguez, C.; Jacobs, J. C; Petrus, E., and Druand, J. B.: The Treatment of Infectious Yaws with One Injection of Penicillin, Bull. World Health Organ. **8**:55-75, 1953.

230. Hill, K. R.: Antibiotics Other than Penicillin in the Treatment of Yaws, Bull. World Health Organ. **7**:108-122, 1953.

231. Csonka, G. W.: Clinical Aspects of Bejel, Brit. J. Ven. Dis. **29**:95-103 (June) 1953.

232. Jones, L. G. G.: "Mutilating" Bejel, Brit. J. Ven. Dis. **29**:104-105 (June) 1953.

233. Cowan, J. A., and Shaw, W. D.: The Venereal Diseases—A Vanishing Problem? J. Michigan M. Soc. **52**:845-848; 886 (Aug.) 1953.

234. Reported Cases of Venereal Disease in the United States Fiscal 1952 and 1953, Pub. Health Rep. **69**:419-421 (April) 1954.

235. Usilton, L. J.; Remein, Q. R.; Thorner, R. M., and Donohue, J. F.: Syphilis Mortality During the Period of the Fifth Revision of the International Lists of Causes of Death, Am. J. Syph. **37**:403-412 (Sept.) 1953.

236. Public Health, Foreign Letters (London), J. A. M. A. **154**:608 (Feb. 13) 1954.

237. Marcussen, P. V.: Variations in the Stability of Sexual Relations as Explanation of Differences in the Spread of Syphilis and Gonorrhea, Am. J. Syph. **37**:355-361 (July) 1953.

238. Costs of Untreated Syphilis, J. Iowa M. Soc. **43**:397-398 (Sept.) 1953.

239. Wilzbach, C. A.: Is Syphilis Under Control? Cincinnati J. Med. **35**:33-34 (Jan.) 1954.

240. Fiumara, N. J.: Venereal Diseases—Present and Future, Am. J. Pub. Health **43**:1443-1451 (Nov.) 1953.

241. Bauer, T. J.: Half a Century of International Control of the Venereal Diseases, Pub. Health Rep. **68**:779-787 (Aug.) 1953.

242. Johnwick, E. B.: The Epidemiology of Venereal Diseases, J. Michigan M. Soc. **52**:849-853; 864 (Aug.) 1953.

243. Fiumara, N. J.: V. D. Control and Prevention, Commonhealth **1**:2-16 (Nov.) 1953.

244. Byrne, E. M.: Contact Interviewing and Investigation, Commonhealth **1**:17-24 (Nov.) 1953.

245. Report of the Study-Group on Syphilis: Sixth World Health Assembly, Chron. World Health Organ. **7**:203-210 (July-Aug.) 1953.

246. Kurlander, A. B., and Carroll, B. E.: Case Finding Through Multiple Screening, Pub. Health Rep. **68**:1035-1042 (Nov.) 1953.

247. Lee, S. S.: Syphilis Reservoir Reduced by Serologic Surveys, Pub. Health Rep. **69**:319-320 (March) 1954.

248. Mason, W. A.: Community Organization for Mass Testing Programs, Am. J. Syph. **37**:362-368 (July) 1953.

249. Shafer, J. K.: Premarital Health Examination Legislation: History and Analysis, Pub. Health Rep. **69**:487-493 (May) 1954.

250. Condit, P. K., and Brewer, A. F.: Premarital Examination Laws—Are They Worthwhile? California Experience with 2,000,000 Examinations, Am. J. Pub. Health **43**:880-887 (July) 1953.

251. El Ghouroury, A. A.: The Syphilis Problem in Asir Province, Saudi Arabia, Bull. World Health Organ. **10**:691-702, 1954.

252. Sachs, S. B., and Selesnick, H.: Bantu Syphilis: An Analysis and Observation on Therapy and Tests, South African M. J. **27**:644-648 (Aug. 1) 1953.

253. Lamont, A. McE., and Blignault, W. J.: A Study of Male Bantu Admissions at Weskoppies During 1952, South African M. J. **27**:637-639 (Aug. 1) 1953.

254. Cutaneous and Venereal Diseases in the Belgian Congo, Foreign Letters (Belgium), J. A. M. A. **153**:873 (Oct. 31) 1953.

255. Berlin, C.: The Problem of Venereal Diseases Among Immigrants, Harefuah **45**:1-2 (July 1) 1953.

256. Sampath, M.: The Influence of Socio-Anthropological Factors on the Incidence of Syphilis in a Heterogenous Group of Pregnant Women in Trinidad, Caribbean M. J. **15**:47-49, 1953.

257. Svendsen, I. B.: Latent Syphilis Ignorée and Syphilis Control During the Epidemic in Denmark, 1942 to 1949: A Statistical Analysis of Newly Diagnosed Untreated Cases, Am. J. Syph. **37**:553-573 (Nov.) 1953.

258. Christiansen, S.: A Report on Syphilis Control in Turkey, Bull. World Health Organ. **10**: 627-690, 1954.

259. Fiumara, N. J.: Results of Investigation of Contacts Reported by Military Service—Massachusetts, 1952, Am. J. Syph. **38**:48-53 (Jan.) 1954.

260. DeMello, L., and Vought, R. L.: The Decline and Fall of Syphilis in New York State, Am. J. Syph. **37**:545-552 (Nov.) 1953.

261. Byington, LeG. B., and Wettig, H., Jr.: A Venereal Disease Epidemiologic Study in Kansas City, Wyandotte County, Kansas, J. Kansas M. Soc. **54**:420-421 (Sept.) 1953.

262. Anderson, S. W.: Venereal Disease Education, United States Navy, Am. J. Syph. **37**:574-576 (Nov.) 1953.

263. Horne, G. O.: The Contemporary Defaulter in a V. D. Clinic: Further Observations, Brit. J. Ven. Dis. **29**:210-212 (Dec.) 1953.

264. Clinical Report of the Rotunda Hospital: Nov. 1, 1951-Nov. 7, 1952, Irish J. M. Sc., pp. 1-52, Dec., 1953.

265. Miller, G. W.: Treponemal Immobilization Test, Queries and Minor Notes, J. A. M. A. **152**: 1500 (Aug. 8) 1953.

Case Reports

FATAL STAPHYLOCOCCAL ENDOCARDITIS TREATED WITH ERYTHROMYCIN

Rapid Development of Resistance in Vivo and in Vitro

ROBERT J. ROANTREE, M.D.
and
LOWELL A. RANTZ, M.D., San Francisco

BECAUSE the Staphylococcus has the ability to develop resistance when exposed to currently used antibiotics, the treatment of staphylococcal disease, and particularly of endocarditis, is most difficult. A recent case well illustrates the emergence of a strain resistant to erythromycin. In vitro studies help to clarify the problem and show that resistant variants may appear from the great majority of staphylococcal strains.

The case described here is of interest from several other viewpoints. The causative organism was a coagulase-negative Staphylococcus albus. Infection was discovered following mitral valvotomy, a fairly rare occurrence,* despite the theoretic probability of such an event. The immediate cause of death seemed to be the occlusion of the mitral orifice by a large vegetation.

REPORT OF A CASE

B. B., a 52-year-old white housewife, reentered Stanford University Hospital on May 11, 1954, for mitral valvotomy. She had undergone rectal polypectomy and cryptectomy on April 7, 1954, without complication. She had a rectal dilatation in the outpatient department on May 3, 1954. Past history included an episode of acute pyelonephritis in 1951 and nocturia for many years. She reported an episode of skin rash due to penicillin.

From the Department of Medicine, Stanford University School of Medicine.

* References 1 and 2.

History.—She had had a transient inflammatory polyarthritis when she was 10. In 1951 she noted shortness of breath which became progressively worse until she could walk only one level block at the time of entry. In late 1951 she suffered a temporary right hemiplegia. Since 1952 she had taken digitalis.

Physical Examination.—The blood pressure was 165/80; the pulse rate was 80, and the temperature was 37.2 C. Positive physical findings included an enlarged heart with a marked systolic heave to the left of the sternum. The rate was 80 and the heart was fibrillating. P_2 was louder than A_2. A loud mitral first sound and an apical diastolic rumble were heard. No systolic murmur was present. Venous distention and pulmonary and peripheral edema were absent.

The laboratory examinations showed a hematocrit value of 48 mm. and white blood cell count of 5,600, with 78% polymorphonuclears. The urinalysis was normal. The electrocardiogram showed auricular fibrillation and abnormal T waves.

Course.—The preoperative course was afebrile. Mitral valvotomy was performed on May 13. The surgeon detected no left auricular clot nor any regurgitant jet. The mitral aperture was estimated at 0.5 cm. in diameter and was widened bluntly. Lingular biopsy was taken and an anal dilatation was done later while the patient was still anesthetized.

Postoperatively no murmur could be heard. Erythromycin, 200 mg. every six hours, and streptomycin, 0.5 gm. per day, were given. A low-salt diet and digitalis were continued. On May 15 the patient's temperature was 39.4 C. and she appeared drowsy. Urinalysis revealed 10 white blood cells per high-power field. Tetracycline, 500 mg. every six hours, was substituted for the previous antibiotics. She continued to have occasional pyuria, but three subsequent urine cultures were sterile. Fever was less but still present, and she complained of weakness and left chest pain. A mild diarrhea, buccal sores, nausea, and vomiting occurred from May 21 to 23 and forced the discontinuance of tetracycline. On

May 26 the hematocrit level was 39 mm., and the hemoglobin was 14.3 gm. The corrected sedimentation rate (Wintrobe) was 45 mm. The white blood cell count was 11,200, and 81% polymorphonuclears. The C-reactive protein was 6 +.

ment of pulmonary edema and an enlarged liver. Salt was restricted to 800 mg. daily and meralluride (Mercuhydrin) sodium was given.

On the basis of the in vitro sensitivity tests, erythromycin, 400 mg. every four hours during the day

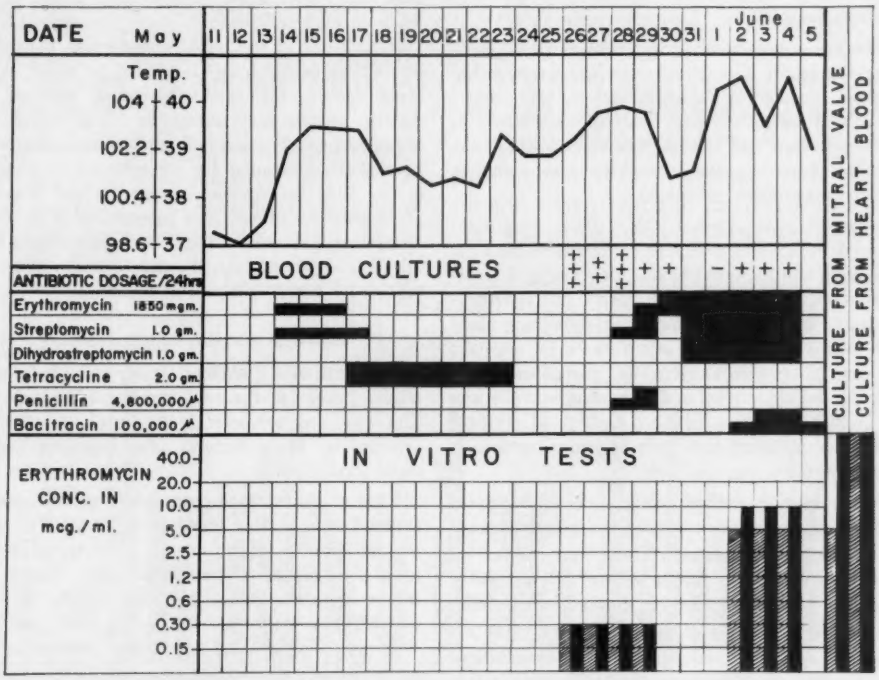


Fig. 1.—Clinical course and laboratory studies of a patient with fatal Staphylococcus endocarditis, following mitral valvulotomy on May 13. In vitro tests: the cross-hatched column indicates the bacteriostatic, and the black column, the bactericidal concentrations of erythromycin.

Sensitivity Tests in Broth with Organisms Isolated from Initial Three Blood Cultures

	Penicillin, Units/Ml.	Bacitracin, Units/Ml.	Erythromycin, γ/Ml.	Chloramphenicol, γ/Ml.	Streptomycin, γ/Ml.
Inhibition	>40	1.25	0.3	5	>250
Killing	>40	2.50	0.3	10	>250

Combination studies

	Penicillin and Bacitracin, Units/Ml.	Erythromycin, γ/Ml., and Bacitracin, Units/Ml.	Erythromycin and Neomycin, γ/Ml.	Erythromycin and Streptomycin, γ/Ml.
Inhibition	0.5 + 1.2	0.15 + 0.15	0.15 + 0.15	0.3 + 10
Killing	0.5 + 1.2	0.3 + 0.3	0.3 + 0.3	0.3 + 10

On May 27 a fresh conjunctival petechia was found. The intramuscular injection of 4,800,000 units of penicillin and 2 gm. of streptomycin daily was begun. Eight blood cultures, taken from May 26 to 28, all yielded a coagulase-negative S. albus, with an antibiotic sensitivity pattern which is shown in the Table. From May 27 to 29 the patient's condition became markedly worse, with the develop-

and 250 mg. intravenously during the night, was begun on May 29. Streptomycin, 1 gm., and dihydrostreptomycin, 1 gm. per day, were added to this regimen. Improvement followed for two days, and, on June 1, the only sterile blood culture was obtained, but, immediately after this, the patient's course again became worse. Electrocardiogram showed a transient auricular flutter with a 2:1

block and an incomplete right bundle branch block. It was suggestive of acute cor pulmonale. A shower of new petechiae occurred on June 3. A precordial systolic murmur was first heard on June 5, and the blood pressure fell to shock levels. Electrocardiogram shortly before death showed complete right bundle branch block.

Autopsy.—The mitral orifice was occluded by a large vegetation. The mitral valve was questionably stenosed. No sign of rheumatic activity was discovered. Multiple emboli with infarcts were found in the left kidney and spleen. The right kidney was the site of an apparently inactive granulomatous process, presumably tuberculous.

Bacteriological Studies.—S. albus, coagulase-negative, was isolated in pure culture from both the vegetation and the heart blood. The results of sensitivity tests are illustrated in Figure 1. Initial screening tests [3] carried out on antibiotic-containing blood agar plates revealed the organism to be resistant to tetracycline, streptomycin, and polymixin at the 10 γ per milliliter level and to penicillin at 0.4 unit per milliliter. It was inhibited by 2 γ of erythromycin per milliliter and 10 γ of neomycin and of chloramphenicol per milliliter.

Broth dilution methods were used to determine more precisely the sensitivity of the Staphylococcus to various antibiotic agents. These were carried out by inoculating 0.05 ml. of an 18-hour culture diluted 1:10 into 2 ml. of peptic liver digest broth containing antibiotics whose effective concentrations are shown in Figure 1 and in the Table. "Inhibition" was indicated by absence of visible growth after 48 hours of incubation at 37 C. "Killing" was said to have occurred if a subculture to broth taken from an antibiotic-containing tube at 24 hours showed no visible growth after an additional 48 hours. A 4 mm. wire loop was used for this transfer to 2 ml. of clear broth.

The Table shows the results of initial antibiotic sensitivities, with selected agents used singly and in combination. Erythromycin appeared to be the most effective single one, since both inhibition and killing occurred at 0.3 γ per milliliter. With erythromycin combined with bacitracin or neomycin, inhibition took place at 0.15 γ per milliliter in the case of each combination but killing required 0.3 γ per milliliter of each. Streptomycin did not reduce either the inhibiting or the killing concentrations.

Figure 1 shows the results of erythromycin sensitivities chronologically. Staphylococci from four blood cultures prior to erythromycin treatment all were killed by 0.3 γ per milliliter. Cultures obtained from the fifth, sixth, and seventh treatment days showed inhibition by 5 γ per milliliter of erythromycin and killing at 10 γ per milliliter. Organisms obtained from the valve and from the heart blood at autopsy were not killed by 40 γ per milliliter, although the valve organisms were inhibited by 5 γ per milliliter.

Because of the rapid appearance of erythromycin-resistant staphylococci in this patient, the organisms from the initial blood culture were tested to see whether resistant variants could be demonstrated. One milliliter of the initial culture was inoculated into 40 ml. of broth and incubated 18 hours. After centrifugation the supernatant was removed by pipette, leaving just enough to allow the packed organisms to be drawn off and spread onto blood agar plates containing 2 γ per milliliter of erythromycin. Six tiny colonies appeared after 48 hours of incubation. These were subcultured onto plates containing 2 γ per milliliter of erythromycin, and all grew well, although the parent strain had been repeatedly killed at this concentration.

FURTHER BACTERIOLOGICAL STUDIES

To determine whether many Staphylococcus strains developed resistant variants when tested in this way, and to ascertain the level of resistance attained by these variants, the following studies were carried out.

Each of 20 strains of coagulase-positive S. aureus isolated from excised tonsils was inhibited by 0.2 γ per milliliter of erythromycin when tested by the usual plate method.[3] These strains were then treated in the same manner as described for the S. albus isolated from the patient, i. e., a very heavy inoculum was spread onto blood agar plates containing 2 γ per milliliter of erythromycin. Small colonies appeared in 24 to 48 hours, and a number of these from each strain were subcultured to plain blood agar plates. Likewise, a bit of the heavy inoculum which was still visible on the surface of the erythromycin plates but which showed no colony formation was subcultured to plain blood agar plates. Growths occurring on the plain plates were then subcultured to blood agar plates containing 2 γ per milliliter of erythromycin and to broth containing serial dilutions of erythromycin, the highest concentration being 40 γ per milliliter. In the broth tests, killing and inhibition were measured as above.

Eighteen of the 20 strains developed from 1 to 13 small colonies when they were exposed to the 2 γ per milliliter erythromycin plates. These colonies and a bit of the inoculum from the same plates were subcultured onto plain blood agar plates. Every transfer, whether from colonies or from persisting inoculum, grew well. When these growths were then subcultured to 2 γ per milliliter erythromycin plates, 41 of the 48 subcultures representing resistant colonies grew well. Only 2 of the 18 representing persisting inocula multiplied.

The degree of resistance attained by a number of the variants is shown in Figure 2. It is note-

worthy that every subculture representing the nongrowing inoculum was inhibited by 1.2 γ per milliliter of erythromycin, the lowest dilution used, although in three cases "killing" required higher concentrations. In contrast to this, only 1 of the 17 growths representing resistant variants was inhibited at this concentration and it was killed only by much larger amounts of the drug. Twelve of the resistant variants were inhibited at the 5 γ per milliliter level, and 7 were killed at this level. The others required higher concentrations.

Comment.—Ninety per cent of the staphylococcal strains were able to develop colonies when exposed to 2 γ per milliliter of erythromycin incorporated in blood agar plates, which was tenfold greater than the inhibitory concentration for the organisms tested in the usual way. Subcultures from these colonial forms showed a definitely higher degree of erythromycin resistance than did subcultures derived from organisms which persisted but were unable to form colonies on the erythromycin containing blood agar.

The degree of resistance developed by the colonial forms was in most cases only twofold to fourfold greater than the 2 γ per milliliter levels used for their isolation, and it was of a magnitude comparable to that developed by the S. albus in the patient. The appearance of these resistant forms is not detected in the usual sensitivity test, because the amount of inoculum used is much less.

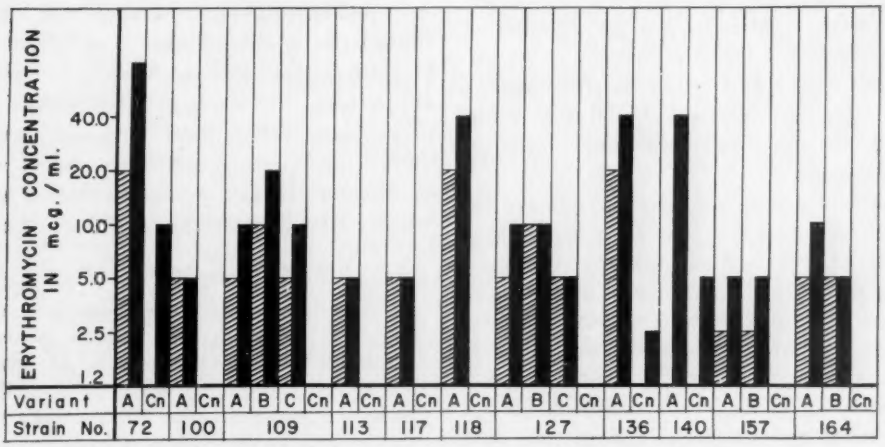


Fig. 2.—Erythromycin sensitivity of variants of strains of Staph. aureus isolated from various sources. Letters (*A, B, C*) indicate variants capable of colony formation in the presence of erythromycin concentrations of 2 γ per milliliter. *Cn* indicates inoculum persisting but incapable of colony formation in the presence of 2 γ per milliliter. The cross-hatched column indicates the bacteriostatic, and the black column, the bactericidal concentrations of erythromycin.

GENERAL COMMENT

Erythromycin-treated Staphylococcus endocarditis has thus far usually ended in death. Of four small series reported † there have been nine failures and one success. The latter was accomplished by treatment with streptomycin and erythromycin combined. A recently reported cure [8] in a case of intraventricular septal defect was accomplished by a combination of streptomycin, oxytetracycline (Terramycin), and erythromycin, the latter used in comparatively high dosage intravenously.

The emergence of erythromycin-resistant staphylococci and streptococci in bacterial endocarditis has been reported in several articles.‡ Resistant staphylococci have been produced in the laboratory both by subculturing on plates with graded increments of erythromycin and by passage through eryth-

† References 4-7.

‡ References 4, 6, and 9.

romycin-containing broth.§ All observers have noted a gradual or small stepwise development of resistance similar to that of penicillin and in contrast to the large, one-step development of streptomycin resistance. Once a high level of resistance to erythromycin has been attained, the Staphylococcus continues to maintain it through at least 10 subcultures on antibiotic-free media.‖ Combination of erythromycin with penicillin or streptomycin has seemed to slow the development of in vitro resistance, provided that each agent has some antibacterial action.[13]

In a study similar to this,[10] a smaller inoculum of one Staphylococcus strain was seeded onto plates containing 1 γ per milliliter of erythromycin. The few colonies which appeared were tested by the variation method of Luria and Delbrück,[14] and the results were interpreted as favoring mutation as the explanation.

Whether these resistant variants are the results of mutation, adaptation to the drug, or selection of highly resistant forms occurring in a normal population of bacteria is an unsettled issue. However, that they have clinical significance seems most likely. In treating Staphylococcus infection it would seem wise to make allowance for the appearance of such forms and to treat with enough antibiotic to afford levels well above those reported as causing inhibition by in vitro testing. Likewise, it is probably worth while to use a second antibiotic which has some action against the organisms, in the hope of preventing the emergence of resistant forms.

There can be no doubt that the number of penicillin-resistant Staphylococcus strains has increased greatly since the introduction of penicillin. These forms seem to retain their acquired resistance over a long period. It is likely, as shown in a recent review,[15] that treatment of Staphylococcus disease at present is less effective than it was immediately after the introduction of penicillin. In a 1952 review of antibiotic-treated Staphylococcus endocarditis,[16] the mortality was about 50%, irrespective of whether the organism was an aureus or albus form, or whether it was coagulase - positive or coagulase - negative. There was a definite positive correlation between a penicillin-sensitive causative organism and cure.

Thus it appears that in many cases penicillin, the most effective antistaphylococcal agent so far developed, has become ineffective. It would seem wise to attempt to protect the more newly developed antibiotics from the same fate insofar as possible. These valuable agents should not be prescribed in cases in which they have no chance of being effective, as in virus disease or in infections in which the bacterium is shown to be resistant to them. The whole question of surgical prophylaxis with antibiotics should be reviewed, and perhaps antibiotics should not be administered in any case in which a reasonably aseptic procedure can be carried out.

§ References 4 and 10-12.

‖ References 4 and 10.

REFERENCES

1. Brunsdon, D. F. V.; Enticknap, J. B., and Milstein, B. B.: A Case of Subacute Bacterial Endocarditis Due to Pseudomonas Aeruginosa Complicating Valvotomy, Guy's Hosp. Rep. **102**: 303, 1953.

2. Stapleton, J.; Harvey, W. P., and Hufnagel, C.: Probable Acute Bacterial Endocarditis Following Valve Surgery, Bull. Georgetown Univ. M. Cen. **6**:5, 1952.

3. Rantz, L. A., and Rantz, H. H.: Sensitivity of Various Clinically Important Bacteria to 4 Antibiotics, Stanford M. Bull. **11**:183, 1953.

4. Haight, T. H., and Finland, M.: Resistance of Bacteria to Erythromycin, Proc. Soc. Exper. Biol. & Med. **81**:183, 1952.

5. Talley, R. W.: Clinical Evaluation of Erythromycin, South. M. J. **46**:1113, 1953.

6. Geraci, J. E., and Martin, W. J.: Antibiotic Therapy of Bacterial Endocarditis: Therapeutic Consideration of Erythromycin, Proc. Staff Meet., Mayo Clin. **29**:109, 1954.

7. Shoemaker, E. H., and Yow, E. M.: Clinical Evaluation of Erythromycin, A. M. A. Arch. Int. Med. **93**:397, 1954.

8. Johnson, T. D., and Hurst, W. J.: Bacterial Endocarditis Due to a Penicillin Resistant Staphylococcus, New England J. Med. **251**:219, 1954.

9. Smith, J. W.; Dyke, R. W., and Griffith, R. S.: Absorption Following Oral Administration of Erythromycin, J. A. M. A. **151**:805, 1953.

10. Hobson, D.: Activity of Erythromycin Against Staphylococcus Aureus, Brit. M. J. **1**:236, 1954.

11. Rajom, P. C., and Adcock, J. D.: Induced Resistance of Staphylococcus to Carbomycin and Erythromycin, Univ. Michigan M. J. **19**:212, 1953.

12. McGuire, J. M.; Bunch, R. L.; Anderson, R. C.; Boaz, H. E.; Flynn, E. H.; Powell, H. M., and Smith, J. W.: Ilotycin: A New Antibiotic, Antibiotics & Chemother. **2**:281, 1952.

13. Purcell, E. M.; Wright, S. S., and Finland, M.: Antibiotic Combinations and Resistance to Antibiotics: Penicillin-Erythromycin and Streptomycin-Erythromycin Combinations in Vitro, Proc. Soc. Exper. Biol. & Med. **82**:124, 1953.

14. Luria, S. E., and Delbrück, M.: Mutation of Bacteria from Virus Sensitivity to Virus Resistance, Genetics **28**:491, 1943.

15. Spink, W. W.: Staphylococcal Infections and the Problem of Antibiotic-Resistant Staphylococci, A. M. A. Arch. Int. Med. **94**:167, 1954.

16. Dowling, H. F.; Lepper, M.; Caldwell, E. R., and Spies, H. W.: Staphylococcic Endocarditis: An Analysis of 25 Cases Treated with Antibiotics, Together with a Review of the Recent Literature, Medicine **31**:155, 1952.

News and Comment

GENERAL NEWS

Birth and Death Rates.—The lowest death rate in the history of the country and the largest annual number of births were forecast for 1954 by Dr. Leonard A. Scheele, Surgeon General of the Public Health Service of the U. S. Department of Health, Education, and Welfare. Dr. Scheele made his statement on the basis of vital statistics reports for the first ten months of the year.

The death rate for the year is expected to close at 9.2 deaths per 1,000 population, a substantial drop from the rates of 9.6 or 9.7 which have prevailed over the past five years. The absence of any reported outbreak of influenza in 1954, with consequent low death rates for the chronic cardiovascular diseases, was cited as a principal reason for the decline. Infant and maternal deaths were also expected to hit new lows.

Births will top the four-million mark for the first time, according to preliminary estimates. The expected birth rate of 25.2 per 1,000 population is the second highest in 28 years and is only 5.3% below the peak year of 1947. A continuing rise in the births of third, fourth, and fifth children is probably responsible for the birth increases in 1953 and 1954. No increase in births of first children was expected, because of falling marriage rates since 1951.

The marriage rate sank to 9.2 per 1,000 population in the first 10 months of 1954, compared with 9.7 for the same period the year before. Low birth rates during the 1930's, resulting in relative scarcity of young people of marriageable age in the present decade, were held chiefly responsible for the marriage decline.

Divorces in the first nine months of 1954 were down 4% from the comparable 1953 period, on the basis of reports from 25 areas. Since the 1946 peak, divorce rates have dropped over 40%.

AUTOIMMUNE HEMOLYTIC DISEASE IN ACUTE LEUKEMIA

ABRAHAM M. FRUMIN, M.D.
and
ALBERT KOHN, B.S., Philadelphia

THE OCCURRENCE of autoimmune hemolytic disease in the leukemias has become increasingly recognized. It is most frequently seen in chronic lymphocytic leukemia [1] and has been described in one case of chronic granulocytic leukemia.[2] We wish to present the first recorded instance in a patient with acute granulocytic leukemia.

R. B., a 26-year-old white woman, was admitted to the Albert Einstein Medical Center, Southern Division, on July 3, 1953, because of weakness and pallor. Five months previously she delivered a normal healthy child, without mishap. A diagnosis of "virus pneumonia" was made a month later because of fever and malaise. Cervical adenopathy was soon noted. A persistent anemia developed two months prior to this hospitalization, which was refractory to various hematinics. She was admitted to another institution, from which, because of inability to type and cross match her blood, she was then referred for evaluation.

From the Department of Research, Albert Einstein Medical Center, Southern Division.

Physical examination revealed a well-developed thin white woman who appeared acutely ill. Marked pallor, without icterus, adenopathy, hepatosplenomegaly, or glossitis, was noted. Slight gingival hyperplasia and an occasional ecchymotic area on the extremities were the only other significant findings.

Blood studies showed RBC, 1,050,000; hemoglobin. 2.8 gm. (18%); reticulocytes, 0.1%; platelets, 70,000; WBC, 65,450, with 1% segmented cells, 9% lymphocytes, 1% metamyelocytes, and 89% blast forms. One nucleated RBC per 100 WBC was seen.

A sternal bone marrow aspiration revealed a good preparation of a markedly hypercellular marrow. The entire marrow was infiltrated by blast cells, with virtually no other formed elements present. Diagnostic impression: acute granulocytic leukemia.

The peroxidase stain of the peripheral blood smear was positive, confirming the impression that these primitive cells were myeloblasts.

An autoantibody was found to be present on the patient's red cells when her blood was initially typed and cross matched. Results of the pertinent immunologic studies are shown in the Table.

Results of Immunologic Studies

	1:1	1:2	1:4	1:8	1:16	1:32	1:64	1:128
37 C.								
AAA*	++++	++++	+++	++	++	+	+	..
1AA	..	..	..	..	..	..	..	..
AAS	..	..	..	..	..	..	..	..
1AS	..	..	..	..	..	..	..	..
22 C.								
AAA	++++	+++	++	++	+	..	..	..
1AA	..	..	..	..	..	..	..	..
AAS	..	..	..	..	..	..	..	..
1AS	..	..	..	..	..	..	..	..
4 C.								
AAA	++	+	..	..	..	..	..	..
1AA	±	..	..	..	..	..	..	..
AAS	+	..	..	..	..	..	..	..
1AS	+	..	..	..	..	..	..	..
Coombs' test	+++	++	++	+	±	..	..	..
Trypsinized RBC	++++	+++	++	++	+	..	..	..

* AAA, autoantibody in albumin; AAS, autoantibody in saline solution; 1AA, isoantibody in albumin; 1AS, isoantibody in saline solution.

The patient was treated with supportive blood transfusions, corticotropin (ACTH), and cortisone, without improvement in her clinical and hematologic picture, and she died on July 19, 1953.

COMMENT

The presence of autoimmune hemolytic disease was first noted in our patient when routine cross matching with the Coombs' reagent demonstrated an autoantibody on the patient's red cells. Immunologic studies showed that this autoantibody was present only in albumin solutions at 37 and 22 C. The direct Coombs' test revealed a titer of 1 : 8. A trypsinized red cell titration showed a value of 1 : 16.

There was no overt evidence of a hemolytic process in the routine hematologic studies. The peripheral blood smear showed occasional spherocytes (?) and no polychromatophilic macrocytes. Rouleaux formation was not present.

The reticulocyte count and serum bilirubin were not elevated. Fecal urobilinogen determinations were attempted but were unsuccessful, owing to inability to collect adequate specimens. It is for these reasons that we prefer to call this a case of autoimmune hemolytic disease rather than hemolytic anemia.

SUMMARY

The first instance of autoimmune hemolytic disease in acute granulocytic leukemia is reported.

REFERENCES

1. Singer, K., and Dameshek, W.: Symptomatic Hemolytic Anemia, Ann. Int. Med. **15**:544-563, 1951.

2. Schumk, G. J., and Lehman, W. L.: Mongolism and Congenital Leukemia, J. A. M. A. **155**: 250-251, 1954.

SIGNIFICANT CASE OF PNEUMOCONIOSIS IN A SOFT-COAL WORKER

LOUIS L. FRIEDMAN, M.D., Birmingham, Ala.

A FATAL case of disabling progressive pneumoconiosis in a soft-coal worker, following removal from further exposure to the etiologic dust, is here presented. Evidence of pulmonary nodulation was lacking in serial roentgenograms of the chest. Massive conglomerate lesions and cavitation without coexisting tuberculosis were demonstrated.

O. L. W., a white soft-coal worker, was 57 years old at the time of his death. He had worked under ground for 29 years. The patient was first seen in this clinic on June 22, 1949. At that time his chief complaints were shortness of breath, cough, and pain in the chest. He first experienced these symptoms during the early part of 1943. In October of that year he was studied in one of the local hospitals by another physician. X-ray examination of the chest at that time (Fig. 1) revealed diffuse symmetrical linear changes throughout both lung fields and emphysema. The patient was treated symptomatically for this illness, which was labeled "chronic bronchitis," and soon returned to his former occupation of drilling in the coal mine. In this work he was exposed to high concentrations of rock and coal dust. He had experienced little or no improvement in his presenting signs and symptoms. The cough and dyspnea increased, and the patient also noticed a moderate, but nevertheless steady, weight loss. Although he suspected that the type of work in which he was engaged was injurious to his health, the patient continued to work in the coal mine, since he lacked training for any other occupation and because of very serious financial limitations. He finally resigned from his job on Jan. 14, 1949, because he was no longer able to complete the amount of work which was required of him. On April 7, 1949, x-ray examination of his chest (Fig. 2) revealed evidence of conglomeration in both upper lobes, with suggestive coalescence in the left midlung field. An increase in the linear changes was noted throughout the remainder of both lung fields. It also appeared that the degree of emphysema had increased on the basis of roentgenographic comparison. Pulmonary tuberculosis was suspected, and the patient was carefully studied in the local tuberculosis clinic. In spite of exhaustive clinical and laboratory studies, this diagnosis could not be substantiated. The patient was informed that he probably had inactive tuberculosis. When he was first seen in this clinic on June 22, 1949, the x-ray was practically identical with that of March 7, 1949. At that time the patient complained of severe dyspnea to the extent that he was compelled to spend most of his time in bed. He was experiencing a severe cough which was irregularly productive of mucopurulent sputum, but there was no hemoptysis. As a rule, the cough was nonproductive and exhausting in nature. He had experienced a recent weight loss and increasing anorexia. The patient had noticed no dependent edema and slept flat in bed. He indicated that this was his most comfortable position. The anterior chest pain was aggravated by coughing and dyspnea. On physical examination, he appeared chronically ill, quite thin, and obviously dyspneic, without any evidence of cyanosis. Aside from the fact that he was edentulous and had varicosities of his lower extremities, the positive physical findings were all confined to the chest, which revealed all of the classic signs of emphysema. The blood cell count, urinalysis, Kahn test for syphilis, stool examination for ova and parasites, and the tuberculin skin test were all negative or within normal limits. Throughout his entire illness the tuberculin skin test remained negative in dilutions of 1:100 and 1:1000. This was true up to the time of the patient's death, on March 31, 1954. The histoplasmin skin test (1:100) was likewise negative. Fluoroscopic examination of the chest confirmed the roentgenographic appearance but in addition revealed evidence of restricted diaphragmatic excursion. The electrocardiogram was essentially normal, but it was suggestive of right heart strain. Ventilatory studies of pulmonary function confirmed the clinical impression of severe emphysema. The spirogram revealed marked abnormality. Facilities for gas analyses were unavailable. Repeated efforts to recover tubercle bacilli from the patient's sputum and gastric contents by means of all known bacteriologic methods of isolation were consistently unsuccessful. From the end of June, 1949, until the patient's death, in March, 1954, he remained under our constant observation. A sympathomimetic-antihistaminic aerosol was prescribed. When indicated, an antibiotic was added to the aerosol in order to combat recurrent bronchopulmonary infection. An expectorant cough preparation, parenteral antibiotic therapy, intravenous aminophylline, and other indi-

From the Friedman Diagnostic Clinic.

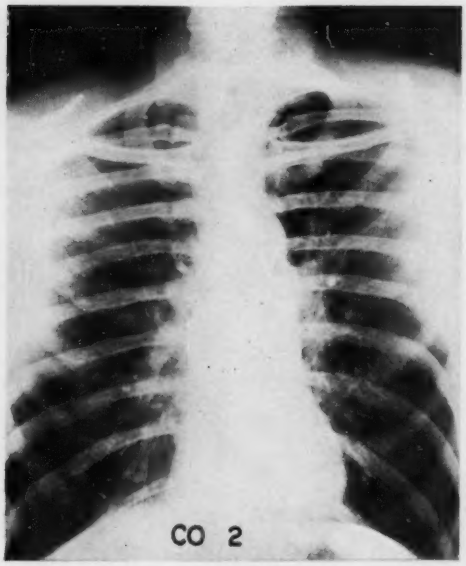


Fig. 1.—CO 2. Initial roentgenogram of the chest. October, 1943. Notice emphysema and linear changes.

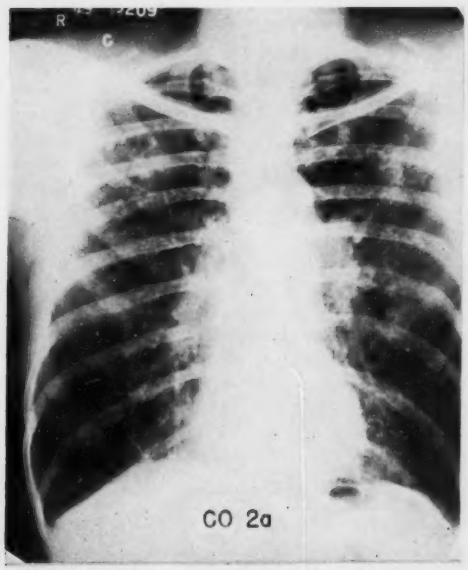


Fig. 2.—CO 2a. April, 1949. Five and one-half years after initial film. Patient out of coal mines since January, 1949. Notice conglomerate densities in both upper lobes, with an increase in emphysema.

cated symptomatic measures were employed as the occasion arose in order to maintain the patient in the most satisfactory respiratory state which could be achieved. Initially, aerosol therapy together with an expectorant cough preparation effectively controlled the patient's distressing respiratory signs and symptoms. This form of therapy was the only treatment which afforded him any satisfactory therapeutic relief since he first became ill, in 1943. Nevertheless, the patient's condition continued to deteriorate, and he required frequent and prolonged

Fig. 3.—CO 2b. October, 1950. Eighteen months later. Notice increase in conglomerate shadows and emphysema.

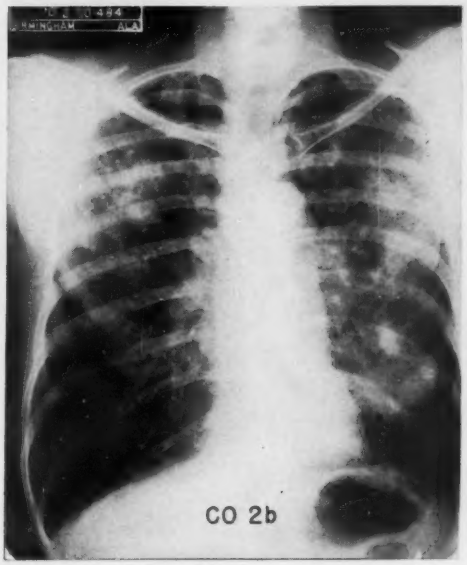
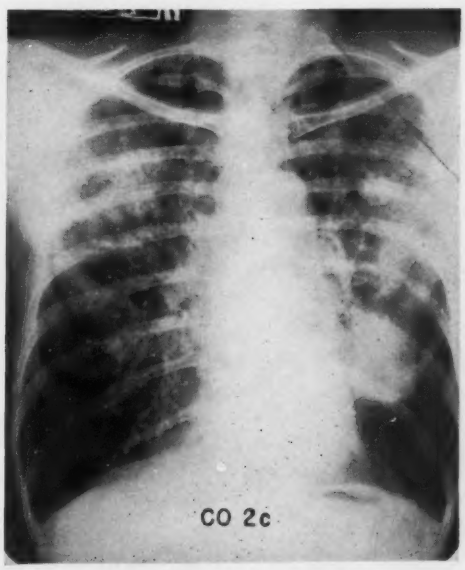


Fig. 4.—CO 2c. August, 1951. Eight months later. Notice progression.



periods of hospitalization in order to reestablish a semblance of respiratory compensation. At one time or another during his prolonged illness the patient received oxygen and oxygen-helium preparations administered by various methods. Intermittent posi-

Fig. 5.—CO 2d. January, 1953. About 18 months later. Notice increase in conglomerate densities and marked compensatory emphysema.

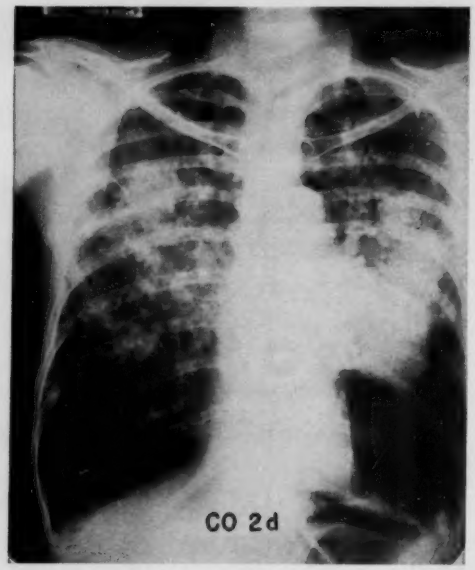
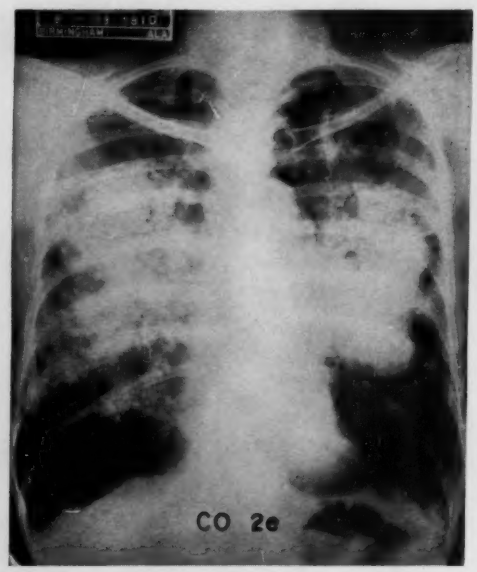


Fig. 6.—CO 2e. Seven months later. Increase in areas of conglomeration, with evidence of definite cavitation at medial end of second anterior and third anterior ribs on left.



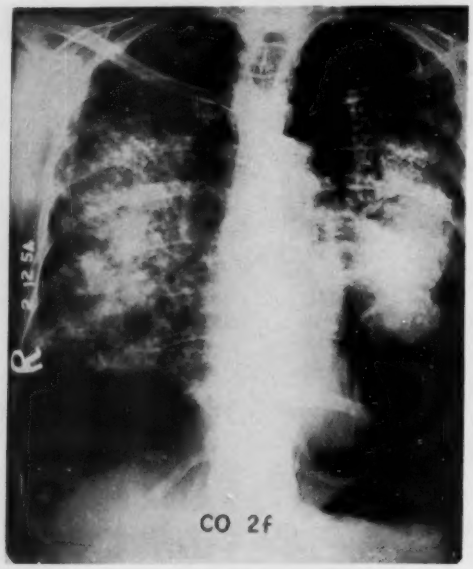


Fig. 7.—CO 2f. Six months later. Patient now had nine months of antituberculous therapy. Notice persistence of cavities.

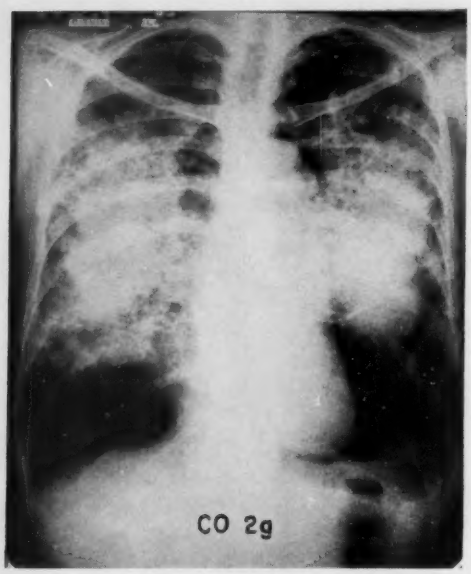


Fig. 8.—CO 2g. March, 1954. Eleven days prior to death.

tive pressure not only failed, but each time following its use the patient's respiratory symptoms were aggravated. Serial roentgenographic examinations of the chest (Figs. 3-8) revealed a relentless progression. The conglomerate areas increased in size, and the patient developed marked compensatory

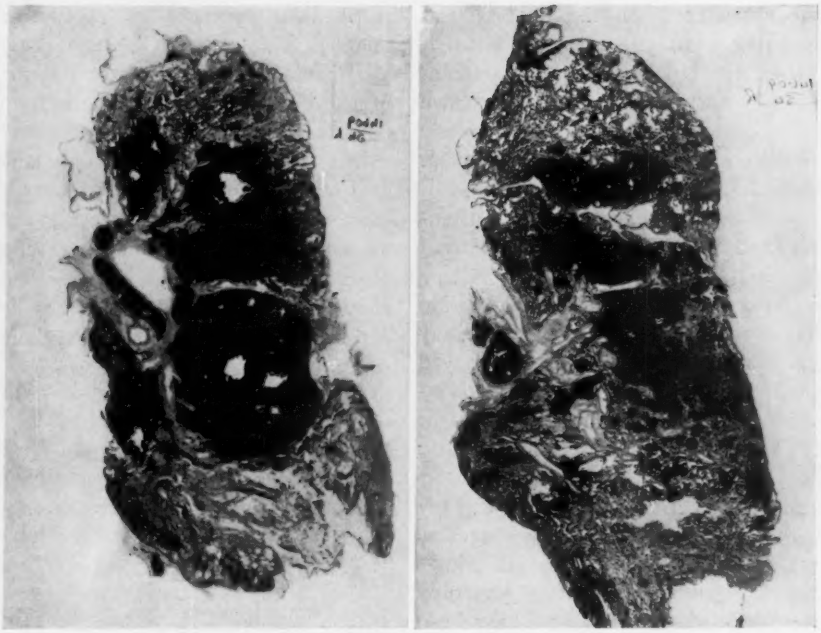


Fig. 9.—Whole lung sections prepared by Dr. J. Gough.

emphysema. In May, 1953, definite cavitation could be seen in the left lung. The patient's weight since he had come under our care had decreased from 147 lb. (66.2 kg.) to 114 lb. (51.3 kg.). Although bacteriologic proof of superimposed tuberculous infection was lacking, isonicotinic acid hydrazide and dihydrostreptomycin were prescribed. These measures were continued in therapeutic dosage up to the time of the patient's death, without any appreciable effect upon the course of his illness either subjectively or objectively. When the patient died, in 1954, he weighed less than 100 lb. (45 kg.). Postmortem examination was performed, and the patient's lungs were sent for histopathologic study to Dr. Jethro Gough, Professor of Pathology, The Welsh National School of Medicine, Cardiff, Wales.

COMMENT

Soft-coal workers' pneumoconiosis is a pulmonary dust disease encountered in soft-coal miners and other soft-coal workers. It results from the inhalation of soft-coal dust, usually in association with varying amounts of silicon dioxide. Contrary to previous empirical teaching, coal dust does not protect the pulmonary tissue against silica but merely alters the tissue response. Certain fractions of coal dust other than silicon dioxide may be fibrogenic. Gough has demonstrated that coal dust relatively free of silicon dioxide may itself produce a crippling and eventually fatal pneumoconiosis.* Inhalation of coal dust with a high concentration of silicon dioxide may result in diffuse symmetrical nodulation typical of classic silicosis. This reaction is relatively uncommon in soft-coal workers' pneumoconiosis. Historically, changes in coal workers' lungs of this nature were probably responsible for the term "anthracosilicosis." Critically disabling pneumoconiosis of soft-coal workers and silicosis may, nevertheless, exist without any roentgenographic evidence of pulmonary nodulation.† Emphysema and diffuse linear changes may be the only roentgenographic manifestations of clinically significant soft-coal workers' pneumoconiosis. It has been my experience and that of other observers that there is poor correlation between chest x-rays and clinical symptomatology in pneumoconiosis.[4] This case demonstrates

* References 1 and 2.

† Reference 5 and Orenstein, A. J., Johnnesburg, Union of South Africa: Personal communication to the author.

that one should rely on the total clinical picture rather than on x-ray examination of the chest for a diagnosis and evaluation of pulmonary dust disease. In this instance histopathologic examination revealed classic discrete silicotic nodules in both lungs (Fig. 9). Nevertheless, in none of the roentgenograms were these nodules manifest. Compensatory and focal emphysema characterized those portions of the lungs not involved by the conglomerate lesions. The observation that clinically significant pneumoconiosis may progress even after the patient is removed from hazardous dust exposure is demonstrated adequately in this case.[4] This patient ceased working in the coal mine in January, 1949, but the disease progressed relentlessly to a fatal outcome. Antituberculosis therapy was instituted because it has been suggested that massive conglomeration usually indicates coexisting tuberculosis.‡ In my study of some 4,000 soft-coal miners, I have been able to confirm the general validity of this conclusion. However, I have observed conglomeration without superimposed tuberculous infection, albeit infrequently. Insofar as it is often impossible to isolate the tubercle bacillus in cases of conglomerate soft-coal workers' pneumoconiosis during life, I felt justified in prescribing specific chemotherapy. This decision became compulsory when definite evidence of cavitation developed (Figs. 6 and 7). More frequently, objective evidence of superimposed tuberculous infection is obtained only after diligent study of the dead tissue. Careful postmortem examination, however, revealed no evidence of tuberculosis in this case, and the observed cavitation was of the ischemic variety. This type of cavitation has been described by Gough [2] and Vorwald [6] and is not uncommon in my own experience.

‡ References 2 and 3.

REFERENCES

1. Gough, J.: Pneumoconiosis in Coal Trimmers, J. Path. & Bact. **51**:277, 1940.

2. Gough, J.: Patterns in Pneumoconiosis, read before the Fourth Conference of the McIntyre Research Foundation, Noranda, Quebec, Canada, Jan. 28, 1952.

3. Gough, J.: Pneumoconiosis in Coal Workers in Wales, Occup. Med. **4**:86, 1947.

4. Hugh-Jones, P., and Fletcher, C. M.: The Social Consequences of Pneumoconiosis Among Coal Miners in South Wales, Medical Research Council Memorandum 25, London, His Majesty's Stationery Office, 1951.

5. Schepers, G. W. H.: Industrial Medicine in South Africa, Ind. Med. **23**:66, 1954.

6. Vorwald, A. J.: Cavitation in the Silicotic Lung, Am. J. Path. **17**:709, 1941.

FELTY'S SYNDROME

Response to Splenectomy After Cortisone Failure

THOMAS J. FITZPATRICK, M.D.
and
LEWIS W. WOODRUFF, M.D., Joliet, Ill.

ALTHOUGH Felty's original description of the syndrome consisting of rheumatoid arthritis, splenomegaly, and leucopenia was published in 1924,[1] it was not until 1932 that hematologic remission following splenectomy was first reported by Hanrahan.[2] Since then, 46 cases subjected to splenectomy have appeared in the literature. In 37 of these the leucopenia was relieved.[3] The rheumatic manifestations, however, have been alleviated inconstantly by the procedure.

The use of the steroid hormones in this disease had been reported only three times prior to the time of this case.* In all of these hematologic and rheumatic remissions were obtained. Normal white cell and differential counts were obtained together with regression of the splenomegaly in each case. However, after cessation of hormone therapy leucopenia, splenomegaly, and arthritic manifestations recurred.

The case herein reported is unusual because of the failure of hematologic response to cortisone with subsequent success following splenectomy.

REPORT OF A CASE

I. J., a 43-year-old white female Danish-born registered nurse, first noted the onset of rheumatoid arthritis in 1938, at the age of 28 years. Initial involvement was of the wrist, metacarpophalangeal, and proximal interphalangeal joints.

In 1939 she received injections of streptococcal filtrate, and in 1940 injections of colloidal sulfur were administered.

In 1941 she was taking about 20 grains (1,200 mg.) of acetylsalicylic acid (Aspirin) daily, with no other form of therapy being used. The white blood cell counts, hemoglobin values, and red blood cell counts for these as well as for the ensuing years are recorded in the Table.

She was seen again in 1946, with involvement of the hands, wrists, ankles, elbows, and knee joints. She averaged about two weeks per year on sick leave from her duties as a nurse.

In 1948 deformities of the metacarpophalangeal and elbow joints were making their appearance. X-rays of the elbow joints are illustrated in Figure 1. During this time she was taking from 20 to 45 grains (1,200 to 2,700 mg.) of acetylsalicylic acid daily.

During the summer of 1952 she developed a perianal abscess, which was followed by a gingivitis with ulcerations of the buccal mucosa.

When examined in October, 1952, she averaged 45 grains (2,700 mg.) of acetylsalicylic acid daily. Physical examination revealed the deformities of her arthritis, splenomegaly, and shotty posterior cervical lymph nodes. The red blood cell count was 2,970,000: hemoglobin, 53%, or 8.35 gm.; white blood cells numbered 2,300, with 36% segmented forms and 64% lymphocytes. The platelets were reported to be in normal numbers on the smear. The sedimentation rate was 42 mm. (Wintrobe method); blood uric acid measured 3.40 mg. per 100 cc., and the Kahn test was negative. Fasting blood sugar was 99 mg. per 100 cc., and the urinalysis showed a specific gravity of 1.020, reaction 9.0, albumin and sugar negative, and an occasional white blood cell.

A diagnosis of Felty's syndrome was made, and she was started on cortisone, 100 mg. orally per day, on Oct. 24, 1952. Complete freedom from pain was obtained within 12 hours of the first dose of the drug. Her comment when seen a week later was,

Fig. 1.—X-rays of right elbow in 1948, demonstrating destruction of cartilage, with narrowing of joint space.

* References 4-6.

"I haven't felt this well in years." No acetylsalicylic acid was necessary for the first time in years.

Maintenance of this status was obtained with an average daily dose of 50 to 75 mg. of cortisone.

By the end of November, 1952, there was a definite decrease in the size of the spleen, although it was still palpable. The maximal response in the white cell count was obtained at this time. The blood cell counts during this time are recorded in the Table. It will be noted that subsequently the white cell count showed a gradual decline, although no decrease in the dose of cortisone was made. The cortisone dose was not increased, because of a slight rise in the diastolic blood pressure to levels of 90 to 95 mm. Hg. There were no other side-effects encountered during the course of treatment.

Through the ensuing months the rheumatic symptoms remained controlled, but it may be seen that the leucopenia continued.

In view of this, she was advised in March, 1953, to have a bone marrow examination preparatory to splenectomy. The bone marrow aspiration was performed by Dr. Steven Schwartz, of Chicago. His report is as follows: "The marrow was moderately hypercellular. Megakaryocytes were intact. Nucleated R. B. C.: W. B. C. ratio was approximately 1:1. Erythropoiesis was normoblastic. Granulopoiesis showed some left shift. There was a moderately marked increase in both reticulo-endothelial cells and eosinophiles. The examination for the lupus erythematosus preparation was negative."

The patient was hospitalized, and splenectomy was performed June 8, 1953. The spleen weighed 740 gm. and measured 20 by 7 by 12 cm. (Fig. 2). The pathological report was as follows: "Splenomegaly with reactive hyperplasia and congestion." Cortisone administration by the intramuscular route was continued during the preoperative and postoperative periods. Her course was smooth, and the white blood cells numbered 6,950 on the second postoperative day (Table).

Blood Studies on Patient I. J.

Date	RBC	Hemoglobin, %	WBC	Neutrophiles, %	Lymphocytes, %
1938	4,710,000	96	6,950	Normal	Normal
1939	4,280,000	86	9,150	Normal	Normal
1940	3,890,000	78	9,100	Normal	Normal
1941	4,290,000	86	8,700	Normal	Normal
1946	.....	93	6,700	Normal	Normal
1948	.....	83	4,950	Normal	Normal
10/20/52	2,970,000	53	2,300	36	64
Cortisone started					
10/31/52	3,000,000	53	2,100	28	66
11/14/52	3,040,000	56	2,500	36	58
11/28/52	3,120,000	60	3,200	66	32
12/19/52	3,260,000	64	1,900	54	44
1/ 2/53	.....	..	2,350	54	44
1/26/53	3,820,000	79	1,350	16	84
2/13/53	3,580,000	73	1,500	28	71
3/20/53	3,660,000	73	1,950	28	72
4/24/53	.....	..	1,050	14	80
5/18/53	4,390,000	13.15 gm.	2,300	24	49
6/ 6/53	3.270,000	65	2,150	48	51
Splenectomy performed 6/8/53					
6/10/53	4,500,000	88	6,950	50	44
6/12/53	4,410,000	88	8,800	71	21
6/26/53	4,400,000	89	5,650	60	33
7/10/53	.....	..	5,150	55	38
8/ 7/53	4,050,000	79	6,200	53	42
9/ 4/53	4,160,000	81	5,450	50	42
10/ 2/53	.....	..	7,000	49	43
11/ 9/53	4,120,000	81	7,200	50	45
12/14/53	.....	..	7,550	52	43

The improvement in the red blood cell count, at least in part, may be due to blood transfusions.

The patient maintained a rheumatic remission for about three weeks postoperatively, during which time the dose of cortisone was reduced step-wise.

The hematologic remission has been complete, the blood cell counts all being normal since operation. No cortisone has been administered since the postoperative period, and the patient is free of any pain. The most recent blood cell counts, on June 7, 1954, showed red cells numbering 4,200,000, with 12.95 gm. of hemoglobin. White cells were 8,700, with

38% lymphocytes, 58% neutrophiles, 3% eosinophiles, and 1% monocytes. Sedimentation rate measured 15 mm. (Wintrobe method).

X-rays of the elbow joint and hand taken five months postoperatively are illustrated in Figure 3.

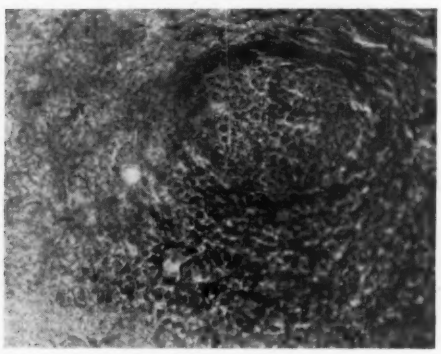
Fig. 3.—X-rays of right elbow and right hand, taken five months after splenectomy and demonstrating the extensive changes of rheumatoid arthritis.

COMMENT

A recent report by Steinberg [3] may indicate why such diverse therapeutic procedures as splenectomy and adrenal steroid hormone therapy should result in suppression of the manifestations of Felty's syndrome. Steinberg reported six cases that responded favorably to splenectomy. One of these was treated with cortisone prior to splenectomy, with resultant prompt disappearance of anemia, leucopenia, and splenomegaly. However, recurrence of these abnormalities resulted upon cessation of treatment. The author noted that both in the experimental animal and in the human splenectomy is frequently followed by hypertrophy of the anterior lobe of the pituitary. This may result in a constant and increased supply of endogenous adrenocorticotropic hormone in the splenectomized person. We have, then, an explanation for the therapeutic success of splenectomy and the adrenal hormones.

An interesting speculation encountered in this patient was whether the leucopenia could have been drug-induced through excessive and constant use of acetylsalicylic acid for many years. This certainly may be a common denominator for cases of Felty's syndrome, since the analgesic effect of acetylsalicylic acid is so widely known and its use is so widespread among rheumatoid arthritis patients. Acetylsalicylic acid is a drug usually prescribed with impunity, because of its apparent lack of toxicity other than the hypersensitivity reactions known to occur in susceptible persons.

Fig. 2.—High-power microscopic section of spleen, which weighed 740 gm. Microscopic report was "reactive hyperplasia and congestion."



Goodman and Gilman [7] state that "The number of red and white cells is not significantly changed by salicylate medication and agranulocytosis has not been reported from their use." Investigation of this problem may be warranted.

The similarity of the hematopathologic manifestations of Felty's syndrome to those of hypersplenism of the Wiseman-Doan [8] type of primary chronic neutropenia of splenic derivation is so striking as to appear to be more than accidental. In this condition, too, splenectomy is therapeutically effective.

The case herein reported showed a good response of the arthritis, but only a slight response of the leucopenia was noted to

cortisone therapy. This was possibly due to the fact that relatively small doses of cortisone were employed.

Another feature which was of interest in this case was the continued administration of cortisone to cover the operative period. Several reports [9] in the recent literature have called attention to the development of acute adrenal cortex insufficiency in the postoperative period in patients who have previously received corticotropin (ACTH) or cortisone.

These hormones exert a suppressive effect on the person's endogenous source of the hormones. Adrenal cortex insufficiency may be precipitated during the postoperative period when the deficient adrenal cortex is called upon to respond to the stress of operation.

It is of vital importance to recognize the potential danger of such an emergency, since the use of the hormones is so prevalent today. It is simple enough to cover the patient during the preoperative and postoperative period by the administration of corticotropin or cortisone.

SUMMARY

A case of Felty's syndrome is reported. Response of the leucopenia to doses of cortisone just sufficient to suppress rheumatic symptoms was incomplete, but splenectomy was followed by a prompt hematological remission. The possibility of chronic acetylsalicylic acid (Aspirin) administration as a cause for the hypersplenism of Felty's syndrome is mentioned.

Miss Bernadine Boecker, Chief Technologist, Silver Cross Hospital, Joliet, Ill., helped in preparing the illustrations.

REFERENCES

1. Felty, A. R.: Chronic Arthritis in the Adult, Associated with Splenomegaly and Leukopenia, Bull. Johns Hopkins Hosp. **35**:16, 1924.

2. Hanrahan, E. M., and Miller, S. R.: Effect of Splenectomy in Felty's Syndrome, J. A. M. A. **99**:1947, 1932.

3. Steinberg, C. L.: Splenectomy in Rheumatoid Arthritis, Ann. Int. Med. **38**:787, 1953.

4. Bichel, J., and Kissmeyer-Nielsen, F.: Felty Syndrome Treated with ACTH (Adrenocorticotrophic Hormone), Acta haemat. **6**:65-70, 1951.

5. Freund, H. A.: Study of Immediate Effects of ACTH (Adrenocorticotrophic Hormone) on Histopathology of Felty Syndrome, J. Michigan M. Soc. **49**:1065-1067, 1950.

6. Hammer, E.: Über die Bieninflussung des Felty Syndrome durch Cortison, Klin. Wchnschr. **30**:90, 1952.

7. Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics: A Textbook of Pharmacology, Toxicology and Therapeutics for Physicians and Medical Students, New York, The Macmillan Company, 1941.

8. Wiseman, B. K., and Doan, C. A.: A Newly Recognized Granulopenic Syndrome Caused by Excessive Splenic Leukolysis and Successfully Treated by Splenectomy, J. Clin. Invest. **19**:473, 1939.

9. Salassa, R. M.; Bennett, W. A.; Keating, F. R., Jr., and Sprague, R. F.: Postoperative Adrenal Cortical Insufficiency: Occurrence in Patients Previously Treated with Cortisone, J. A. M. A. **152**:1509, 1953.

PERIODIC DISEASE

Report of a Case of Recurrent Abdominal and Thoracic Pain with Synchronous Gross Hematuria

EDMUND SHWAYRI, M.D.
and
NEVIN TUTUNJI, M.D., Beirut, Lebanon

FOR A NUMBER of years reports have appeared of a variety of disorders characterized by repetition of similar events. These may begin in early life and recur at regular, predictable intervals of days, weeks, or months or at irregular intervals. The episodes of disease may recur for decades; they may cease temporarily or permanently, and the general health rarely is disturbed. In early observations, the recurrence of the episodes at regular intervals in many cases led to the introduction of the term periodic disease.[1] However, exact periodicity often is absent, as noted previously [2] and in 58 patients studied at the American University Hospital.[3] Furthermore, it remains to be seen whether the different varieties of periodic disease described have anything more in common than the mechanism underlying recurrence.

According to Reimann and his associates, the only variety of periodic disease encountered in Lebanon is the form characterized by episodes of abdominalgia.[3] It is hereditary in many instances and affects especially people of Armenian, Arabic, and Jewish extraction. In many of the patients abdominalgia is associated with pain in the chest, and in some victims episodes of stethalgia occur alone. The abdominal pain presents a diagnostic problem in differentiating the disorder from other acute intra-abdominal conditions, especially acute appendicitis and acute cholecystitis. Because of the similarity in symptoms and signs and the presence of neutrophilic leucocytosis, many of the patients had undergone one or more surgical operations. In some of these cases, congestion, loss of the smooth shiny character of the peritoneum, and a small amount of sterile fluid were found. Microscopically there was mild acute exudative inflammation of the peritoneum. Though the condition is usually benign, death during episodes has been reported in several instances by others. The cause is unknown, and necropsy in a few fatal cases gave no clue. In one series of cases the disease was complicated by "nephropathy" in eight members of a family, and of these four died in uremia.[4] The present report deals with a hitherto undescribed peculiarity in a case of periodic disease, namely, synchronous bloody urine.

From the Department of Medicine, American University of Beirut.

REPORT OF CASE

In August, 1952, fifteen months before admission to the hospital, an Arab youth, aged 20, had colic lasting 24 hours accompanied by loose stools. The pain started abruptly, involved the entire abdomen, increased in intensity, and was accompanied by fever. There were three or four soft stools. Six weeks later he had a similar attack. A third episode occurred after a week. Several such episodes then came at monthly intervals. In January, 1953, appendectomy was performed. Ten days after operation, fever and arthralgia appeared and lasted three months. During this time and afterward, episodes of abdominalgia came first at monthly intervals and then gradually at shorter periods until the cycles were of seven or eight days, for a time coming on Sundays. Since June, 1953, the episodes have been accompanied by a new feature, bloody urine.

The patient was admitted to the hospital on Nov. 19, on the medical service of Dr. H. A. Reimann, having had an episode four days before. No abnormalities were found on examination. There were no telangiectatic areas. The urine was normal in color and revealed a trace of albumin and microscopic hematuria.

On Sunday, Nov. 22, an episode began on schedule, seven days after the preceding one. At 8 a. m., the first sign was an increase of the pulse rate from 70 to 95. At 11 a. m. there was a prickling sensation in the precordium, which within an hour or two developed into severe pain made worse on

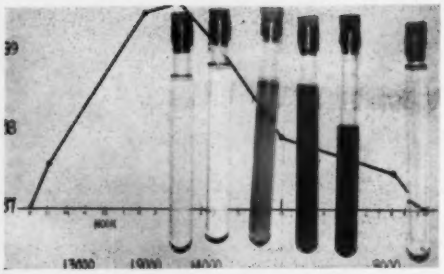


Fig. 1.—A 26-hour episode. The fever reached its height in nine hours; the leucocytes rose from normal to 13,000 and 19,000. During the first five hours of defervescence the urine was clear, but it abruptly became bloody six hours after the acme of fever, remained so for about eight hours, and promptly cleared.

inspiration. No friction was audible. There was no abdominal pain during this episode. The pulse rate increased to 110, and the temperature rose from normal to 38.2 C. (101.8 F.). By 4 p. m. it reached 39.4 C. (102.9 F.). The leucocytes, which numbered 9,000, with 68% polynuclear cells, on admission, rose to 16,000, with 80% polynuclear cells, during the first day. Fever and leucocytosis diminished steadily until they became normal after 24 hours. Pain gradually disappeared. The urine, clear yellow before, became cloudy and red about six hours after the temperature had reached its peak and in six more hours was smoky brown with blood. Several hours later it again became clear except for a few erythrocytes seen microscopically (Fig. 1).

A second observed episode came seven days later, Nov. 29. This one began, at 9 a. m., with pain in the right upper quadrant. By 4 p. m. the patient was flushed, sweating, holding his abdomen, and moaning with pain. The abdominal muscles were rigid, and there was tenderness in the right upper quadrant. The pain spread to involve all the abdomen and radiated to the back. It was exaggerated by deep inspiration. The urine became bloody as usual.

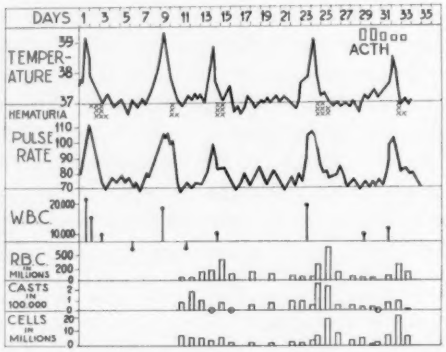
Episodes observed or recorded thereafter came at intervals varying between 5 and 14 days, as shown in Figure 2. On one occasion there was only a slight elevation of temperature but no pain or hematuria; on another there was fever and hematuria but no pain. In different episodes the pain began in different areas, in the right or left side of the chest but most often in the right upper quadrant of the abdomen. There was at no time any evidence of bleeding in the skin, nose, gums, or respiratory or alimentary tracts. The tourniquet test gave a slightly positive result, but there was no unusual bleeding from sites of venipuncture.

A course of adrenocorticotropic hormone therapy was given, starting with 100 mg. of corticotropin daily and diminishing to 25 mg. over a period of 4 days, and was continued for 10 days. The drug was given by the intramuscular route. Its administration was followed by the usual eosinopenic response. Following this treatment two mild episodes occurred; then there have been no further episodes to date. One examination of the urine during this period revealed few red blood corpuscles.

Laboratory Studies.—Leucocytosis (white cells 15,000 to 20,000), with about 80% polymorphonuclear cells, occurred during most episodes. In the free intervals the cell count was normal. The sedimentation rate by the Cutler method was moderately elevated, from 15 mm. per hour during the free interval to about 25 mm. per hour during an episode. The hemoglobin was 15 gm. per 100 cc., and the erythrocytes averaged 4,500,000 to 5,000,000 per cubic millimeter. The reticulocytes numbered 0.5 to 1% and did not rise during or after an episode. The fragility of erythrocytes was normal during and between episodes; hemolysis began at 0.46 and was complete at 0.30. The bleeding time was four minutes; the coagulation time was normal. The serum calcium was 10.8 mg. per 100 cc.; inorganic phosphorus, 4.2 mg. per 100 cc.; cholesterol, 215 mg. per 100 cc.; glucose, 82 mg. per 100 cc.; urea nitrogen, 13 mg. per 100 cc. The serum bilirubin never was elevated above 1 mg. per 100 cc., and no change occurred during or after the episodes.

The urine during free intervals contained a faint trace of albumin and, seen on microscopy, a few erythrocytes and, occasionally, casts. The bloody urine did not contain bilirubin, and a protein-free filtrate had a normal color. In ultraviolet light the fluorescence of normal urine was observed; hence porphyrins were believed to be absent. Exposure of the urine to sunlight caused no change. Addis counts were made daily or every other day during three cycles, as shown in Figure 2. All countable components of the urine increased during the episodes.

Fig. 2.—Five episodes of fever and abdominalgia, tachycardia, and leucocytosis, with concurrent bloody urine. Addis counts were made during a period covering three episodes.



Cystoscopy and catheterization of the ureters was attempted during a free period to determine if the blood were coming from one or both kidneys. The urinary bladder and mouth of the ureters appeared normal. Urine obtained from the right ureter contained few erythrocytes. No urine could be obtained from the left one. This probably was due to suppression of urine formation associated with the catheterization, since pyelography showed good function on that side. The patient refused to allow further study of the left ureter. Although it is believed that blood comes from both kidneys, it was not possible to prove it.

Several intravenous pyelograms showed normal kidneys and ureters. There was no evidence of stone, tumor, or tuberculosis. Cholecystograms were normal. Gastrointestinal and thoracic ronetgenography showed nothing abnormal.

The patient has five sisters and a brother. Two sisters have periodic abdominalgia and, like the patient, had had appendectomy. In one, aged 27, episodes of abdominalgia and fever began at the age of 12. They recur irregularly at intervals of one, two, or three months. No urinary changes occur. In the other, aged 22, similar episodes began at the age of 14. They last 24 to 48 hours, without changes in the urine, and recur in one-, two-, or six-month cycles. During one year there were no episodes. Episodes occurred with greater frequency during each of four pregnancies. This is in contrast with patients reported elsewhere, in whom episodes ceased during pregnancy.[2] Single samples of urine from 19 genetic members of three generations of the family contained no erythrocytes; nor was there any history of abnormal bleeding or other hematologic anomaly.

COMMENT

The case described is typical of periodic abdominalgia but has hematuria in addition. Studies failed to reveal any lesion of the genitourinary tract or vascular system or any abnormality of hemostatic function. The proportion of the abnormal urinary constituents as well as the course of the disease did not resemble those of any of the usual forms of nephritis. The leucocytes and casts accompanying the red blood cells are accounted for by the passage of whole blood. In Figures 1 and 2 the striking rhythmic urinary changes appear during the phase of subsidence of episodes. The time from the onset of an episode to the first appearance of bloody urine is longer than that required for the passage of urine from Bowman's capsule to the bladder. This lag cannot be explained. Gross bleeding evidently occurs for a short time only.

In other cases of periodic disease, no abnormalities were demonstrated in the intervals between episodes.[2] The present case, therefore, is unique and acquires a new interest because hematuria is constant but increases suddenly and greatly during the episodes. This suggests continuous activity of some unknown process in this patient. However, the urinary abnormality may be caused by factors other than periodic disease and may only be exaggerated during the episodes.

The hereditary nature of periodic abdominalgia as noted in the present case is evident.[3] Other examples of recurrent hematuria, called congenital familial hematuria, were observed many years ago.* Episodes of hematuria, of epistaxis, or of hematemesis in these cases often began shortly after birth. They came at irregular intervals of weeks, months, or years. There was fever, malaise, and aches in the head, back, and limbs lasting several days. The urine became bloody and contained casts six hours after the onset of fever. Albuminuria and microscopic hematuria persisted. Anemia did not occur, and the victims were otherwise well for years, except one who died from acute nephritis. No telangiectasia was reported in these families, but hereditary hemorrhagic telangiectasia is a cause of recurrent hematuria in others.[7]

It is uncertain if the case described here has any points in common with the diseases just mentioned or with the cases of periodic abdominalgia and renal disease described by Mamou and Cattan.[4] In their cases the intensity of the albuminuria was not reported to fluctuate in rhythm with the abdominal episodes, and hematuria was not mentioned.

SUMMARY

Periodic disease with fever, abdominalgia, and/or stethalgia in a youth of 20 was associated with synchronous bloody urine. No

* References 5 and 6.

cause was found to account for the renal bleeding. Hematuria in periodic disease has so far not been described. Therapy with adrenocorticotrophic hormone seemed to influence the course of the disease. Two sisters have periodic disease.

REFERENCES

1. Reimann, H. A.: Periodic Disease: A Probable Syndrome Including Periodic Fever, Benign Paroxysmal Peritonitis, Cyclic Neutropenia and Intermittent Arthralgia, J. A. M. A. **136**:239-244 (Jan. 24) 1948.

2. Reimann, H. A.: Periodic Disease, Medicine **30**:219-245 (Sept.) 1951.

3. Reimann, H. A.; Moadie, J.; Semerdjian, S., and Sahyoun, P.: Periodic Peritonitis: Heredity and Pathology, J. A. M. A. **154**:1254-1260 (April 10) 1954.

4. Mamou, A., and Cattan, R.: La maladie périodique: Sur 14 cas personnels dont 8 compliqués de nephropathies, Semaine hôp. **28**:1062-1070 (April 2) 1952.

5. Guthrie, L. G.: "Idiopathic" or Congenital, Hereditary and Family Haematuria, Lancet **1**:1243-1246 (May 3) 1902.

6. Aitken, J.: Congenital, Hereditary and Family Haematuria, Lancet **2**:444-446 (Aug. 14) 1909.

7. Campbell, J. L.: Hereditary Hemorrhagic Telangiectasia as a Cause of Haematuria: Two Case Reports, J. Urol. **62**:80-88 (July) 1949.

OSTIAL STENOSIS OF CORONARY ARTERIES IN NINE-YEAR-OLD GIRL

N. GOORMAGHTIGH, M.D.
L. DE VOS, M.D.
and
A. BLANCQUAERT, M.D., Ghent, Belgium

OSTIAL stenosis of the coronaries in young children is extremely rare. It was found only twice in a series of 14,000 consecutive autopsies performed at the Johns Hopkins Hospital (Norris [1]), a percentage of 0.014.

In the case to be described the histology of the lesion points to a syphilitic origin but there is no corroborating evidence provided by the history, the serological tests, or the presence of other stigmata of congenital syphilis.

REPORT OF A CASE

Clinical Data.—The patient, a girl 9 years and 9 months old, was born of apparently healthy parents. She had a sister 7 years old. She had become listless, had shown disinclination for food, and had lost weight. She coughed occasionally. At the end of June, 1952, severe abdominal pain occurred suddenly, followed almost immediately by convulsions. The child became unconscious and a little feverish. The spinal fluid showed no abnormalities. X-ray of the lungs suggested the possibility of miliary tuberculosis. The heart shadow was normal. The Pirquet reaction was positive.

Two days later the child recovered consciousness but complained of precordial pain. She was short of breath. Another x-ray film, taken 7 weeks later, showed an increased heart shadow. The electrocardiogram revealed a left strain; precordial leads were not taken. The liver was enlarged. The diagnosis of miliary tuberculosis complicated by tuberculous pericarditis was made, and cardiotonics were added to the treatment with streptomycin, *p*-aminosalicylic acid, and isoniazid (Rimifon).

The heart shadow continued to increase in size, and premature beats were recorded on the electrocardiogram. The lower extremities became swollen, and the urine contained albumin, urobilin, and bilirubin.

From the Departments of Pediatrics and of Pathology, University of Ghent.

On admission to the pediatric department (University of Ghent) on Dec. 4, 1952, the general condition of the patient was very unsatisfactory; she had severe dyspnea, pallor, anasarca, ascites, and splenomegaly. The heart sounds were loud, and there was a splitting of the second sound and, from time to time, a gallop rhythm. The electrocardiogram showed signs of left hypertrophy, with a relatively high R_I and a deep S_{II} and S_{III}, slightly widened QRS complexes (0.09 second), biphasic T_I, and a visible but not very deep Q_I. In the precordial Lead V_2 there was an rS wave, an S-T segment above the base line, and a high T wave. Finally, there was a shifting of the transitional zone towards the left (Lead V_5). Although a Q_I and a diphasic T_I may suggest the presence of a myocardial infarction, there were no signs of infarction in the precordial leads (no Q-S wave). Only the relatively low voltage of Lead V_5 could perhaps be interpreted as a "border effect." Unfortunately no Lead V_6 was taken.

The blood pressure was 100/70. The venous pressure, measured in the external jugular vein, was 11 cm. H_2O.

X-ray examination showed a greatly increased heart shadow with little pulsation and a reticular image of the lungs. Two attempts to drain the pericardial sac by puncture were unsuccessful.

The laboratory tests gave the following results:

Urine: Nucleoalbumin, positive; serum albumin, positive; reduction, negative; acetone, negative; indican, negative; urobilin, negative; bilirubin, slightly positive; benzidine, slightly positive. Sediment, a few erythrocytes, no Koch bacilli; culture on Löwenstein medium, negative.

Blood: erythrocyte count, 2,650,000; hemoglobin, 70%; differential count: 1% eosinophiles, 79% polymorphonuclears (segmented?), and 20% lymphocytes; sedimentation: 6/20.

Blood Chemistry: Urea, 0.35 gm.; total serum proteins, 4.35 mg. per 100 ml., albumin 2.1 mg., α_1-globulin 0.3 mg., α_2-globulin 0.7 mg., β_1-globulin 0.48 mg., β_2-globulin 0.17 mg., γ-globulin 0.6 mg. per 100 ml.

Total lipoids: 506 mg. per 100 cc.; calcium: 8.2 mg. per 100 cc.; phosphorous: 3.65 mg. per 100 cc.; phosphatase: 8 units per 100 cc. (Bodansky); liver-function tests: cephalin-cholesterol, 3+/3+; thymol turbidity, 3.5 units; $ZnSO_4$, 4.1 units; $(NH_4)_2SO_4$, 2.9 units; bilirubin, 2.2 mg. per 100 cc.

Meinicke and Bordet-Wasserman tests: negative.

Empty stomach fluid: no Koch bacilli by direct examination or after culture on Löwenstein medium.

Cold agglutination: negative.

Serological tests for rheumatic fever: Antistreptolysin titer, 400 units (normal up to 250 units); L. agglutination, 0 up to 1/40; O. agglutination, 1/80 (normal up to 1/80)*; Rose test, 1/64 (normal up to 1/8).

Digitalis treatment seemed to improve the condition; dyspnea practically disappeared but the second heart sound remained split. On the morning of Dec. 12, 1952, another attempt at washing the stomach to search for tubercle bacilli was made. Soon after, the girl became again very dyspneic and restless. The precordial leads of the electrocardiogram now showed relatively low QRS complexes in the precordial leads, which

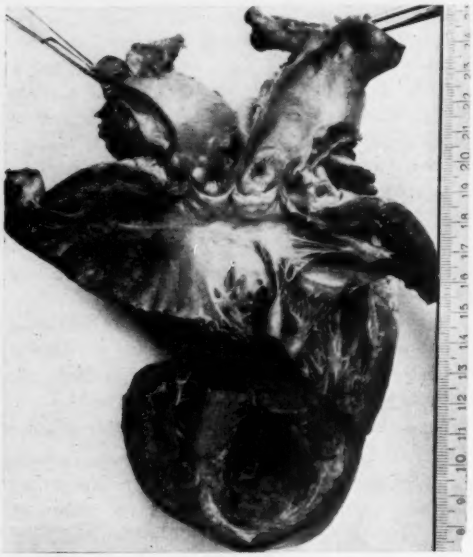


Fig. 1.—A view of the narrowed ostia of the coronaries. Near the apex there is a scar in the myocardium.

were all of the RS type and had an almost identical appearance, probably as the result of a pericardial effusion.

The child died in the late afternoon.

It is of interest to note that three months after the child's death the mother gave birth to a normal baby. The mother never had abortions.

Autopsy Report.—Body weight, 30 kg. Body length, 140 cm. The pericardium contained about 50 cc. of hemorrhagic fluid. There was marked hypertrophy of the heart (330 gm.), dilatation of the heart cavities, bilateral hydrothorax (300 cc. of fluid on each side), and old fibrous adhesions of the apex of both lungs. There were more recent adhesions of the right lung to the diaphragm. The lungs were soft and springy. On section they showed the presence of numerous small poorly delineated brown patches. Weight of the right lung was 420 gm.; weight of the left, 320 gm. Ascites and passive congestion of the abdominal organs were noted.

Detailed examination of the heart (Fig. 1): A pin-prick wound caused by intracardial injection of epinephrine (Adrenalin) during the agony was found on the anterior side of the left ventricle. The apex was covered by a thin layer of fibrin. The dilated heart cavities were filled with clots. The wall of the left ventricle was markedly hypertrophied; that of the right ventricle, less so. Part of the medial muscular layer of the left ventricle on the anterior side had become a scar which extended towards the apex, where the inner layer also had become fibrotic. It was covered by a flat grayish thrombus. The ductus arteriosus and the foramen ovale were closed. All the valves were smooth.

The most striking change concerned the ostia of the coronary arteries. Each was surrounded by an annular thickening of the intima of the aorta. The left ostium was closed; the right one admitted a probe 1.5 mm. thick. These circular cushions touched each other on the posterior side of the aorta and were united on the anterior side by a fibrous band 3 mm. wide. As a result, the bulbus aorta was narrowed. At the level of the ostia the circumference of the vessel measured 3.7 cm., while at the insertion of the semilunar valves it attained 5 cm.

The origin of the left coronary artery was reduced to a solid string about 1 cm. long. Further on, the coronary artery was patent but its lumen was markedly narrowed. Beyond its narrowed ostium the right coronary artery and its ramifications were patent and even widened. The openings of the Thebesian veins in both atria were conspicuous.

This description applies, of course, to a terminal stage. The sequence of events had probably been as follows: There was hypertrophic scarring of the bulbus aortae, involving the margin of both ostia of the coronary arteries and causing a moderate degree of aortic stenosis. Hence, there was compensatory hypertrophy of the left ventricle. At

* The O-agglutination test (Thulin) is based on a reaction of the antibodies in the patient's serum with a somatic antigen of hemolytic Streptococcus. The test is positive in rheumatic fever, although not so often and not so soon as the antistreptolysin test. The L-agglutination test (Thulin) is an agglutination test that uses a "surface antigen" of hemolytic Streptococcus. The test is positive in rheumatoid arthritis.[20]

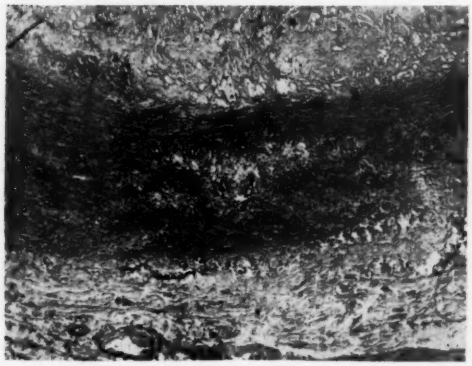


Fig. 2.—Microphotograph showing the thickened and fibrotic adventitia (below). There are vascular neoformation, scarring, and patchy destruction of the elastic lamellae. Above, the sclerotic intima.

a later stage, both ostia became narrow. For a time there was compensatory circulation via the right coronary artery (Blumgart, Schlesinger, and Davis [2]) and reversed circulation in the Thebesian veins (Wearn [3]) both of which became gradually ineffective. Heart dilatation, lung congestion, and insufficiency of the right heart followed. Probably when the ostium of the left coronary artery was completely obliterated and stenosis of the right ostium became extreme scarring of the anterior wall

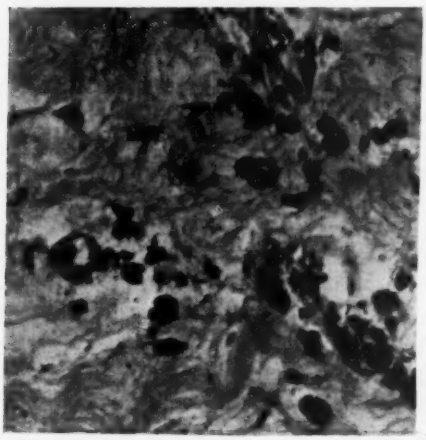


Fig. 3.—Perivascular infiltration of plasmocytes in the adventitia.

of the left ventricle developed and insufficiency of the right heart increased.

We suggest that the abdominal crisis occurred at this stage. It was in fact an angina pectoris attack. The convulsions which accompanied the attack are best explained by the sudden and increased failure of the left ventricle combined with aortic stenosis. What looked like miliary tuberculosis of the lung on the x-ray film corresponds in reality to innumerable small foci of stasis (histological confirmation).

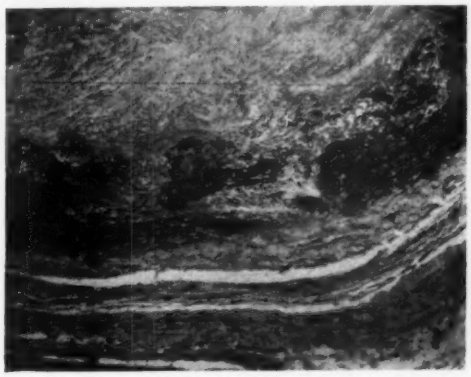
Histology. — In microscopic preparations of the thickened rings around the ostia of the coronaries sectioned along their diameter the severe damage to the media was revealed: scattered scars containing a few lymphocytes and histiocytes; disruption and patchy destruction of the elastic lamellae. Those that were left were coarse and undulated

Fig. 4.—More intensive scarring of the media.

(Figs. 2 and 4). Close to the ostium a very small segment of the media had undergone calcification, but it must be emphasized that its structural pattern was still recognizable. On hematoxylin and eosin preparations the elastic fibers stained deeply with hematoxylin, while the destroyed muscle fibers lying between them were converted to pale blue uniformly stained bands.

The adventitia was thickened and fibrotic (Fig. 2). The muscular coating of the vasa vasorum was hypertrophic. There was vascular regeneration. Around the adventitial vessels lymphocytes and plasmocytes were found in small numbers (Fig. 3).

Fig. 5.—Chronic acquired syphilitic aortitis in an adult, for comparison.



Newly formed capillaries penetrated into the media and reached the deeper layer of the intima. The intima, which was increased in volume, consisted of two layers: (*a*) a deep one, with coarse collageneous lamellae, calcium deposits, amorphous and crystalline lipid material (some of it positive with the Smith-Dietrich stain), and foam cells, which also infiltrated the media; (*b*) a superficial one, with fine collagenous fibrils and proliferating stellate endothelial cells.

When one compares the lesions represented in Figures 2 and 4 with those of acquired syphilitic aortitis (chronic stage, Fig. 5) in the adult and keeps in mind their localization at the ostia of the coronary vessels the similarity is striking. However, no spirochetes were found with the Levaditi technique. The small areas of calcification of the media which were observed must be distinguished from those found in "coronary calcinosis." The proliferation of stellate cells in the upper layers of the intima has, in our view, nothing to do with a rheumatic component, since fibrinoïd necrosis of the ground substance and its sequelae were absent.

COMMENT

It is known that children of syphilitic parents, who are stillborn or who die soon after birth, can show syphilitic lesions of the aorta along with syphilis in other organs (Hennig,[4] Mracek,[5] Rach and Wiesner,[6] Klotz,[7] Rebaudi[8]). As a rule, the involvement of the aorta is detected only microscopically. In Klotz's case[7] the lesions were macroscopic (inner surface of the aorta wrinkled, blood suffusions); microscopic examination showed nodular and plasmocyte infiltration in the media and adventitia. Spirochetes are easily found (Rebaudi[8]). These cases offer no problem.

On the contrary, in older children and young adults the existence of congenital syphilis is more difficult to prove clinically. Stolkind[9] is prepared to accept this diagnosis if the following conditions are fulfilled: a hereditary anamnesis, the presence of other stigmata of congenital syphilis, positive serological tests, and typical lesions in postmortem examination. Few if any of the reports in the literature give this mass of evidence. However, some fulfill in part the conditions laid down by Stolkind.

In 1877 Barlow[10] thought that the cerebral arteries could be damaged in congenital syphilis. His observations concerned an infant 7 months old, with syphilitic parents. However, it is von Zetkowsky's[11] observation dating from 1916 that inaugurates the subject we are discussing. The postmortem examination of a girl 17 years of age who had been treated for congenital syphilis in her childhood revealed mesoaortitis with stenosis of the coronaries and an aneurysm of the abdominal aorta as large as a fist. The Wassermann test of the serum of the cadaver was strongly positive.

In 1932 S. McDonald Jr.[12] published a case of mesoaortitis in a boy of 9 years. His father had been treated since 1925 for tertiary syphilis. The obvious stigma of hereditary syphilis in the child was an interstitial keratitis. He received injections of arsphenamine (Novarsenobillon) for six weeks, and he died of acute yellow atrophy of the liver. For a distance of 2.5 cm. above the aortic cups the intima showed gross changes suggestive of syphilis. The coronary arteries and the thoracic and iliac arteries showed no gross anomaly. The heart weighed 185 gm. No spirochetes were found in the aortic lesions (Levaditi stain). It should be noted that death was not due to the coronary lesion.

In a second paper, published two years later, the same author[13] deals with a series of 11 young adults presenting aortic lesions. Some had a history of acquired syphilis, but in at least 4 hereditary syphilis seemed plausible. Cases 2 and 3 are of special interest. They concern, respectively, a young man of 21 years and his sister, who was 19. Their father had locomotor ataxia at the time. The boy died suddenly. On hearing the news his sister collapsed, and she died soon after. In both were found the morphological signs of aortitis with occlusion of the ostia of the coronaries. In these two remarkable cases there is a definite hereditary history of syphilis and a convincing postmortem report. The fact that the same aortic lesions occurred in two children of a tabetic father seems to rule out acquired syphilis.

Of the 11 cases reported by McDonald 9 showed either a slight narrowing of the ostia of the coronary artery or a marked ste-

nosis or a complete unilateral or bilateral occlusion. In all these cases the morbid anatomy pointed to a syphilitic disease; in four the evidence was in favor of congenital syphilis; in one (Case 11) there was a history of acquired syphilis. Norris' cases,[1] published in 1935, are similar to ours. There was considerable narrowing of the ostia of both coronaries in a 9-year-old girl; there was occlusion of the right ostium and stenosis of the left in a boy of 17. Both died suddenly. The blood Wassermann reaction of the girl was positive. The mother of the girl had 17 pregnancies. The first children were stillborn; of the remainder only seven were still alive. The father was recovering from a stroke at the time of the children's death. With regard to the boy no tests could be made. The mother refused to be tested.

The localization of syphilitic disease at the ostia of the coronaries is well known and has been investigated again in recent years by Moritz,[14] who reviews the literature of the subject and makes the interesting point that syphilitic inflammation of the origin of the coronary artery is not limited to that part of the artery that is included in the wall of the aorta. It extends generally along 1 cm., starting from the ostium. Also in our case the left coronary was occluded over a distance of 1 cm. from its origin.

In many cases ostial stenosis of the coronaries coexists with aneurysms of the aorta, which in the adult nearly always are caused by syphilis. A few reports of aneurysms of different sections of the aorta in children or young adults have come to our notice. Paul[15] reviewed the literature of the subject up to 1922 and discussed a personal case. He lays particular stress on von Zetkowsky's publication, to which we have already referred. In his opinion, this author was the first to prove decisively the existence of a late hereditary vascular syphilis. Paul mentions also Baginsky's (1908) case of a girl 7 years old in which there was chorioretinitis, aneurysm of the abdominal aorta, and a histologic picture of mesoaortitis; no Wassermann test was made. There was also ulcerative endocarditis, the significance of which was not made clear. An almost similar observation of Nixon (1912)* is commented on. The stigmata of congenital syphilis consisted of the presence of Hutchinson's teeth. But Stolkind[9] questions the value of this sign, since Hutchinson's teeth can also be present in rachitis.

Mention is also made of a postmortem report of Wilson and Marks,† who found a ruptured aneurysm of the aorta ascendens in a child 4 years old. The histologic diagnosis was mesoaortitis syphilitica. Paul's own case (1922) concerning a girl of 20 was diagnosed after autopsy examination as mesoaortitis syphilitica causing multiple aneurysms. Remarkable is the fact that also the ostium of the left coronary was occluded. The hereditary history is suggestive of syphilis. The mother had been pregnant 11 times. Two children were stillborn. Three died soon after birth. Only three children remained alive; two among them were twins. The Bordet-Wassermann and Meinecke tests in the father were both strongly positive and corroborated the tentative diagnosis of syphilis congenita tarda although the serological tests in the child were negative. Neiman and Marks[16] found four aneurysms of the aorta ascendens and the aortic arch in a 10-year-old girl. The serological tests for syphilis in the parents were negative. On the evidence of the histological examination they admitted the possibility of hereditary syphilis.

As has been already emphasized, the difficulty in the way of a firm diagnosis is the fact that the histologic findings are not always supported by the serological tests or by the family history. When a child or young adult dies as the result of ostial stenosis of the coronaries the apparently mild syphilitic inflammation can have died down, as in our case. It is the site of the healing lesion which causes fatal outcome. Spirochetes are never found in the aortic lesions in children or young adults in whom late congenital syphilis

* Nixon, J., cited by Paul.[15]

† Wilson and Marks, cited by Neiman and Marks.[16]

is suspected. One may therefore expect that the serological tests have become negative.

The possibility of syphilis of the second generation should also be discussed. Much has been written for or against this notion since Fournier and his son introduced it in the medical literature. The problem is reviewed objectively in Pautrier's [17] contribution to the third volume of the "Traité de médecine" (1951). To begin with, he admits, on strong clinical evidence, the existence of late congenital syphilis (lues congenita tarda). As to the existence of congenital syphilis of the second and even third generation his conclusions can be summarized as follows: one cannot deliberately and systematically reject it, but one should not admit such a diagnosis as easily as was done in the past. Serological tests made repeatedly by reliable technicians will be of great diagnostic value if they are found to be positive in successive generations at an age when acquired syphilis can be ruled out. In his opinion it is on this basis that the problem of syphilis of the second generation should be restudied. Pautrier relates a series of family histories which make the notion of congenital syphilis of the second generation probable, although he agrees that they do not afford a definite proof. The perusal of some of these histories seems to show that in one of the generations the disease can be inapparent (masked). This was already suggested by earlier observers. Another possible explanation of the discrepancy between the positive morphological findings and the negative serological tests in the parents consists in postulating an accidental contamination soon after birth. That such an early contamination is possible is proved by an observation of Stolkind,[9] who observed a chancre on the lip in a suckling. According to Norris,[1] the occurrence of an aortic lesion nine years after the primary infection is not impossible. He refers to the paper of Maynard and associates, who estimate the average span between primary infection and aortic disease at 22.7 years but state that it is only 10 years in 10% of cases. Norris found cardiovascular involvement at postmortem examination in an adult Negro two years after contamination.

The notion of a postnatal contamination confronts us with new difficulties. It could only be accepted if the manifestations of the primary (cf. Stolkind's case) and secondary stages of the accidentally acquired disease have been recorded.

The observation of McDonald Jr.[12] of a brother and sister whose father was tabetic at the time of their death is not in favor of a postnatal contamination.

Our personal opinion can be summarized as follows: for the pathologist the aortic and coronary lesions described in this paper are caused by a syphilitic inflammation. On the other hand, the clinicians concerned with this case are more cautious. On the one hand, the negative blood tests of the parents and of their deceased 9-year-old girl and the 7-year-old living girl as well as of the baby born after the eldest girl died and, on the other hand, the lack of symptoms of syphilis in the parents and their two surviving children justify this attitude.

The data of the adjoining Table are not conclusive but show the frequency of a family history of syphilis, supported or not by positive blood tests, in most of the few cases reported in the literature.

Contrary to the data of this Table, in our case neither the clinical observation of the parents nor the results of their serological tests suggests the possibility of congenital syphilis.

Taking into account the negative blood tests in the parents of our patient, who so far have enjoyed good health (no abortions) and have two surviving children apparently normal (negative blood tests) we must be dealing with a disease process of still unknown etiology or with a still debated second generation syphilis. The results of the Bordet-Wassermann and the Meinecke tests in the grandparents are as follows: paternal grandfather, negative; paternal grandmother, negative. The maternal grandfather is supposed to have died from pneumonia at the age of 58, and the maternal grandmother, from "Parkinsonism?" at the age of 38. The

latter diagnosis is rather vague. In our view these incomplete data do not allow us to exclude definitely the existence of syphilis in one of the grandparents. As to a postnatal infection, we reject it on the basis of the absence of clinical signs of primary and secondary syphilis in a well-looked-after child.

Unfortunately, we have had no opportunity to apply the Nelson test.

During the young patient's life the possibility of a rheumatic etiology has been considered. Antistreptolysin titer and the Rose test were both unquestionably positive. Consequently, the child has been in contact with hemolytic streptococci. But the tests would have been of greater value if we had information about the results of the tests at the onset of the disease.

Anyhow, the lesions of the aorta and of the ostia of the coronaries do not substantiate the assumption of a rheumatic etiology. We did not find Aschoff cells or Aschoff bodies, which are characteristic of the disease (Pappenheimer and von Glahn [18]).

In view of the interest that had arisen in recent years in "coronary calcinosis" in children, this item is briefly discussed. After one reads Stryker's [19] paper, it is evident that this is a disease quite different from the one we are concerned with here. The coronaries are involved in their entire length. Other arteries are calcified at the same time. In our case a very small part of the media was calcified, but it had a diffierent aspect from the lesion observed in coronary calcinosis in infancy. The structure of the media was still recognizable, whereas the figures of Stryker's [19] paper show apparently amorphous calcium deposits resembling those seen in hypervitaminosis D.

The clinical study is made difficult not only by the small number of cases but also by the fact that a fair percentage of the children or young adults die suddenly, apparently without prodromal symptoms. When such young patients have come under observation the correct diagnosis has practically never been made before death. If, as the result of the publication of our report, pediatricians become aware of the existence of this rare vascular disease and of the possibility of a syphilitic etiology, one may hope that clinical investigation will be conducted more thoroughly along a definite path and that finally we shall know whether the disease is always syphilitic or not. If not, we shall have to conclude that some cases at least of ostial stenosis in children and young adults constitute a new morbid entity, which we would have to call "idiopathic" as long as the etiologic agent is not discovered.

Ostial Stenosis of the Coronary Arteries

	Concomitant Lesions	Sex	Age, Yr.	Symptoms of Congenital Syphilis	Blood Test in Patient	Symptoms in Parents	Blood Test in Parents
von Zetkowsky, 1916 [11]	Aneurysm, abd. aorta	F	17	+	++ (cadaver)	Mother treated for syphilis	—
Paul, 1922 [15]	Aneurysms, thor. and abdom. aortas	F	20	—	—	3 pregnancies, stillborn or premature death	Father ++
McDonald Jr., 1932 [13]	.....	M	9	Interstitial keratitis	Not done	Father treated for tertiary syphilis	Father +
McDonald Jr., 1934 [18]	.....	M*	21	—	Not done	Father	Not
		F*	19	—	Not done	tabetic	done
Norris, 1935 [1]	.....	F	9	—	+	17 pregnancies, 3 stillborn	Not done
	.....	M	17	—	Not done	?	?

* These patients were brother and sister.

SUMMARY

A report is made of a case of ostial stenosis of the coronary arteries in a girl 9 years, 9 months old.

The histological picture is that of tertiary syphilitic aortitis limited to the region of the ostia and the origin of the coronary arteries.

The histological findings are corroborated neither by the clinical examination of the parents nor by the blood tests in the parents and their children nor by the blood tests in the surviving grandparents.

The possibility of second generation syphilis or of accidentally acquired syphilis is discussed.

From the clinical point of view a non-syphilitic etiology is not ruled out.

REFERENCES

1. Norris, R. F.: Bull. Johns Hopkins Hosp. **57**:206, 1935.

2. Blumgart, H. L.; Schlesinger, M. J., and Davis, D.: Am. Heart J. **19**:1, 1940.

3. Wearne, J. T.: J. Exper. Med. **47**:293, 1928.

4. Henning, E.: Jahrb. Kinderheilk. **30**:106, 1890.

5. Mracek, F.: Arch. Dermat. u. Syph., Supp. 273, 1893.

6. Rach, E., and Wiesner, R.: Wien. klin. Wchnschr. **20**:521, 1907.

7. Klotz, O.: J. Path. & Bact. **12**:11, 1907.

8. Rebaudi, S.: Monatschr. f. Geburtsh. u. Frauenh. **35**:681, 1912.

9. Stolkind, E. J.: Brit. J. Child. Dis. **17**:126, 1920.

10. Barlow, T.: Tr. Path. Soc. London **28**:287, 1877.

11. von Zetkowsky: Inaugural Dissertation, Giessen, 1916.

12. McDonald, S., Jr.: Brit. J. Ven. Dis. **8**:263, 1932.

13. McDonald, S., Jr.: Brit. J. Ven. Dis. **10**:183, 1934.

14. Moritz, A. R.: Arch. Path. **11**:44, 1931.

15. Paul, F.: Arch. path. Anat. **240**:59, 1928.

16. Neiman, B. H., and Marks, M. B.: Am. J. Dis. Child. **59**:571, 1940.

17. Paurier, L. M., in Lemierre, A., and others: Traité de médecine: Vol. 3. Tuberculose, cancer, maladie de Besnier-Bœck-Schaumann, syphilis, by J. Bretey and others, Paris, Masson & Cie., 1951.

18. Pappenheimer, A. M., and von Glahn, W. C.: J. M. Res. **44**:489, 1924.

19. Stryker, W. A.: Am. J. Path. **22**:1007, 1946.

20. Thulin, K. E.: Acta path. et microbiol. scandinav., Supp. 75, p. 1, 1948.

TREATMENT OF HEMOCHROMATOSIS BY MASSIVE VENESECTION

Report of a Case Treated by Removal of Forty Liters of Blood in Twenty-Eight Months

RALPH M. MYERSON, M.D., Philadelphia
and
IRVIN N. CARROLL, M.D., Wilmington, Del.

HEMOCHROMATOSIS is an uncommon disease of uncertain etiology occurring predominantly in males and characterized by extensive deposition of iron throughout the body. Although the liver, pancreas, and skin are chiefly involved, significant iron accumulation may be present in lymph nodes, testes, heart, and adrenals. Of all the organs, the brain alone is said to be spared.[1] Clinically, hemochromatosis is characterized by cirrhosis of the liver usually accompanied by diabetes and pigmentation of the skin. Asthenia, loss of weight, and hypogonadism are frequently present.

It seems fairly well established, particularly by radioiron absorption studies, that the underlying defect in hemochromatosis is a disturbance in the normal intestinal mucosal iron-blocking mechanism, resulting in excessive iron absorption regardless of the saturation of the body stores.* Since there is no active mechanism, except for hemorrhage, by which iron can be excreted,† a gradual increase in tissue iron saturation occurs. As a result, the total body iron content, normally 3 to 5 gm., may be increased to 50 gm., with particularly heavy concentration in the pancreas, liver, and skin.‡ The serum iron level is elevated, and there is usually 100% saturation of the iron-binding β-globulin fraction of the serum proteins, in comparison with the average 30% saturation found normally.

The rarity of hemochromatosis in women before the age of menopause suggests that the loss of blood in menstruation and parturition may be sufficient to delay or suppress the clinical manifestations of the disease. In view of the lack of any excretory mechanism for iron, phlebotomy has been employed recently in an attempt to mobilize and utilize the excess tissue iron present in hemochromatosis. Hahn and his co-workers were the first to employ this technique, in connection with their studies on radioiron absorption.[9] Massive long-term phlebotomy for hemochromatosis was initiated by Davis and his associates § and Howard, Balfour, and Cullen [8] in 1947 and by Finch and his coworkers [12] in 1948. In 1951 Beyers and Gitlow reported a patient similarly treated.[13] Recently, Davis and Arrowsmith compiled 30 cases of hemochromatosis treated by venesection.[14] In 12 of the 15 patients considered "verified" by virtue of careful follow-up, the response was considered satisfactory. Since this review, additional successful results have been reported.‖

A patient treated by venesection, with removal of more than 40,000 cc. of blood during a period of 28 months, with improvement, is presented at this time.

REPORT OF CASE

R. B., a 34-year-old white man, was admitted to the Veterans Administration Hospital, Wilmington, Del., on Feb. 6, 1952. For two months prior to admission he had noticed a progressive development of weakness and weight loss, associated with paroxysmal attacks of pain in the back and abdomen. About two weeks prior to entry polyuria, polydipsia, and intractable vomiting began. The symp-

From the Medical Services, Veterans Administration Hospitals, Philadelphia and Wilmington, Del.

* References 2-5.

† References 6 and 7.

‡ References 1, 2, and 8.

§ References 10 and 11.

‖ References 5 and 15-18.

toms persisted and progressed, and on the day prior to admission the patient lapsed into coma. There had been no history of any change in skin pigmentation, but the patient had noticed decreased libido for several years.

The past history was not remarkable. There was no known family history of diabetes or hemochromatosis.

On admission the patient was critically ill, comatose, cachectic, and markedly dehydrated. There was a prominent odor of acetone on his breath, and the respirations were Kussmaul in type. The lungs were clear. The heart was not enlarged; the rhythm was totally irregular, with an apical rate of 160 per minute; no murmurs could be heard. The blood pressure was 80/60. The abdomen was held rigidly; the liver could be felt 8 cm. below the right costal margin; the spleen was not palpable. The testes were atrophic. There was a generalized brownish discoloration of the skin, most prominent in the exposed portions. Large patches of dark brown pigmentation were present around the genitalia and on the shins. The body hair was scant.

Initial laboratory studies revealed 4 + glycosuria and acetonuria. The blood sugar was 420 mg. per 100 cc.; CO_2-combining power, 4 mEq. per liter; serum chlorides, 75 mEq. per liter; blood urea nitrogen, 20 mg. per 100 cc. The white blood cell count was 30,900, with 86% polymorphonuclear leucocytes. The red blood cell count was 5,420,000; hemoglobin, 20 gm. An ECG revealed rapid auricular fibrillation, with tall, peaked T-waves suggesting hyperkalemia.

The patient responded well to vigorous therapy for diabetic coma. His heart rhythm spontaneously reverted to a normal sinus mechanism with a normal rate. The diabetes was eventually controlled on a 3,200 Cal. diet (carbohydrate, 400 gm.; protein, 130 gm.; fat, 120 gm.) and a total of 95 units of insulin daily. Further studies after stabilization of the patient's diabetes revealed serum total proteins of 8 gm., with 4.2 gm. of albumin, 3.8 gm. of globulin; cephalin and thymol-flocculation tests were negative. Prothrombin time was 100% of normal; cholesterol, 180 mg. per 100 cc., with 105 mg. of esters; alkaline phosphatase, 4.0 Bodansky units. There was no retention of sulfobromophthalein (Bromsulfalein) after 45 minutes. The red blood cell count averaged 4,800,000; the hemoglobin, 14.5 gm. The white blood cell count was normal, with an essentially normal differential count. Subsequent ECG's, roentgenograms of the chest and gastrointestinal tract, and intravenous urogram revealed no findings of significance. A liver biopsy, performed on Feb. 25, 1952, revealed portal fibrosis consistent with a moderately advanced cirrhosis of the liver. Prussian blue stains revealed a large amount of iron within both the hepatic parenchymal

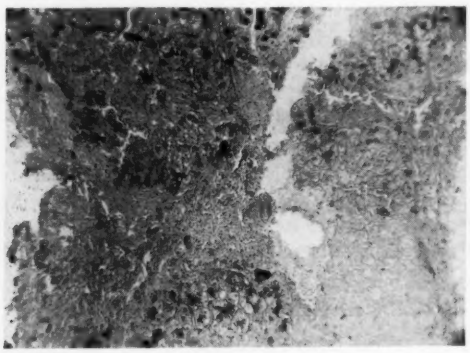
Phlebotomies and Serial Laboratory Data in Reported Case

Date	Blood Removed, Cc.	Blood Removed, Cumulative Total, Liters	Hemoglobin, Gm./100 Ml.	RBC, Millions/Cu. Mm.	Hematocrit, %	Reticulocytes, %	Serum Proteins, Gm./100 Ml.			Insulin, Units/Day
							Total	Albumin	Globulin	
3/52	1,125	1.1	12.0	4.1	41	0.7	8.9	5.4	3.5	96
4/52	2,695	3.8	12.0	4.0	41	1.8	8.4	5.2	3.2	85
5/52	2,475	6.3	11.5	3.8	40	1.2	8.4	5.4	3.0	68
6/52	2,925	9.2	11.5	3.9	40	1.2	8.6	5.4	3.2	68
7/52	2,300	11.5	11.0	3.6	39	0.8	8.2	5.1	3.1	68
8/52	3,000	14.5	11.0	3.6	..	...	8.2	5.2	3.0	68
9/52	2,375	16.9	10.0	3.4	..	0.2	8.2	5.4	2.8	68
10/52	1,950	18.8	14.0	4.7	..	0.8	...	...	...	68
11/52	1,900	20.7	13.0	4.4	..	0.6	8.6	5.2	3.4	68
12/52	1,750	22.5	11.0	3.6	39	...	...	...	...	68
1/53	1,250	23.7	12.0	4.0	..	...	...	...	...	68
2/53	750	24.5	12.5	4.5	..	...	...	...	...	68
3/53	950	25.4	12.5	4.2	..	...	...	...	...	55
4/53	1,450	26.9	12.0	3.8	40	0.6	8.4	5.0	3.4	55
5/53	0	26.9	14.5	4.8	..	...	...	...	...	55
6/53	0	26.9	....	...	..	...	...	...	...	55
7/53	1,700	28.6	....	...	..	...	...	...	...	55
8/53	1,400	30.0	10.5	3.5	..	0.6	8.6	5.4	3.2	55
9/53	950	31.0	11.5	3.7	39	...	...	...	...	55
10/53	1,100	32.0	12.0	4.0	..	...	...	...	...	55
11/53	1,200	33.2	....	...	..	...	...	...	...	55
12/53	1,000	34.2	....	...	..	...	...	...	...	55
1/54	1,400	35.6	13.5	...	42	...	9.1	5.5	3.6	55
2/54	1,000	36.6	12.5	4.2	41	0.8	...	...	...	55
3/54	1,500	38.1	....	...	..	...	...	...	...	55
4/54	1,000	39.1	....	...	..	...	...	...	...	55
5/54	1,100	40.2	....	...	..	...	...	...	...	55

cells and the fibrotic tissue (Fig. 1). A serum iron level was 280 γ per 100 cc. The iron-binding globulin was completely saturated.

The diagnosis of hemochromatosis was felt to have been well established, and therapy with weekly phlebotomies was begun in March, 1952. Between 500 and 1,000 cc. of blood was removed at weekly intervals. It was exceedingly difficult to provoke an anemia, despite which the highest reticulocyte count noted was 1.8%. Difficulty in finding satisfactory veins was frequently a factor in limiting the amount of venesection. Despite this, the patient was very cooperative, in fact, enthusiastic regarding the therapy. He stated that he noted rapid subjective improvement and soon became asymptomatic and gained weight and strength. Undoubtedly this early improvement was due to control of his diabetes and improvement in his state of nutrition. As phlebotomies were continued, a gradual decrease in liver size, noticeable decrease in pigmentation, a return of libido, and apparent amelioration of diabetes took place. Despite the fact that the patient's plasma was not reinfused, the serum total proteins remained unchanged, averaging 8.4 gm., of which approximately 5 gm. was albumin, 3.4 gm. globulin. Liver biopsies showed a progressive decrease in the amount of iron deposition. The latest biopsy, performed in January, 1954, revealed only a scattered trace of iron remaining in the fibrotic areas. The hepatic cells appeared to be free of iron. There had been no appreciable change in the amount of fibrosis (Fig. 2). The serum iron level in January, 1954, was 128 γ per 100 cc. There was 30% saturation of the iron-binding β-globulin at this time. During the course of phlebotomy therapy the patient's insulin requirements decreased to 55 units daily. At the present time the patient is gainfully employed and is entirely asymptomatic. Phlebotomy, with removal of 1,000 to 1,500 cc. of blood per month, is being continued.

Fig. 1.—Microscopic appearance of liver in March, 1952, before institution of phlebotomy therapy. The dark areas represent iron granules stained with Prussian blue stain.



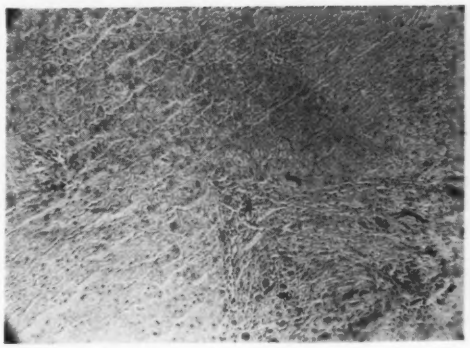


Fig. 2.—Microscopic appearance of liver in January, 1954, after removal of about 35 liters of blood. Only a small amount of iron deposition remains in the periportal fibrotic tissue. (The photomicrograph depicts the area of the slide showing the maximal amount of iron.)

COMMENT

During a 28-month period a total of 40 liters of blood was removed from R. B., representing a loss of 20 gm. of iron. The resultant decrease in serum iron and degree of iron-binding saturation, lessening of skin pigmentation, and diminution in the amount of liver iron is evidence of the mobility of the excess tissue iron. The difficulty in provoking an anemia by massive phlebotomy indicates the availability of the accumulated iron for the formation of hemoglobin. Though no decrease in the amount of liver fibrosis has been demonstrated, it seems safe to assume that phlebotomy and the removal of excess tissue iron has had a favorable influence on the usual downhill course of this disease. The patient is asymptomatic and less pigmented, libido is returning, and a decrease in his insulin requirements has occurred.

Though some constitutional defect may be responsible for both the accumulation of iron and the fibrosis seen in hemochromatosis, attempts have been made to relate the two aspects of the disease. As yet, the role of the excess iron in the production of the widespread fibrosis and functional impairment has not been established. Hemosiderosis, the excessive deposition of iron in the tissues, has been reproduced in experimental animals by large parenteral doses of iron and blood

administration.¶ No great success, however, has been achieved in this manner in the production of tissue fibrosis except in the presence of unusual nutritional disturbances.# The work of the Gillmans * suggests that similar factors may operate in the etiology of the hemochromatosis seen in South African natives.

The relationship of idiopathic hemochromatosis to the exogenous type of hemochromatosis seen following multiple transfusions or associated with certain anemias is highly controversial and unsettled.† Some factor other than administered blood or iron released by hemolysis seems probable in the production of exogenous hemochromatosis. Its occurrence after an insufficient number of transfusions to account for the amount of tissue iron accumulated ‡ and its association with "refractory" or aplastic anemias seem significant.§ It is possible that the anoxia due to the anemia results in a disturbance of intracellular metabolism making the cell more susceptible to the deposition of iron. The recent observations of Kleckner, Baggenstoss, and Weir [29] would seem to indicate that idiopathic hemochromatosis and transfusional hemosiderosis are separate and distinct clinical and pathological entities.

SUMMARY

A case of idiopathic hemochromatosis is presented in which repeated phlebotomy, with removal of 40 liters of blood, has been employed over a period of 28 months.

During this period substantial clinical improvement has occurred, as manifested by the patient's state of well-being, decrease in skin pigmentation, return of libido, and apparent amelioration of diabetes. Serial liver biopsies have demonstrated a marked decrease in the amount of liver iron, although the fibrosis appears unchanged. The high serum iron and total saturation of the iron-binding β-globulin have returned to normal values.

The difficulty in provoking an anemia is evidence of the availability of the tissue iron stores for the production of hemoglobin.

Although there is no direct evidence for the relationship of the excess tissue iron and the fibrosis seen in hemochromatosis, the removal of iron by phlebotomy seems to have a favorable effect on the usual course of this disease.

Dr. Bruce Barnes and the staff of the Nanticoke Memorial Hospital, Seaford, Del., performed most of the venesections.

REFERENCES

1. Sheldon, J. H.: Haemochromatosis, London, Oxford University Press, 1935.

2. Granick, S.: Iron Metabolism and Hemochromatosis, Bull. New York Acad. Med. **25**:403, 1949.

3. Dubach, R.; Callender, S. T., and Moore, C. V.: Studies in Iron Transportation and Metabolism: VI. Absorption of Radioactive Iron in Patients with Fever and with Anemias of Varied Etiology, Blood **3**:526, 1948.

4. Alper, T.; Savage, D. V., and Bothwell, T. H.: Radioiron Studies in a Case of Hemochromatosis, J. Lab. & Clin. Med. **37**:665, 1951.

5. Peterson, R. E., and Ettinger, R. H.: Radioactive Iron Absorption in Siderosis (Hemochromatosis) of the Liver, Am. J. Med. **15**:518, 1953.

6. McCance, R. A., and Widdowson, E. M.: Absorption and Excretion of Iron, Lancet **2**:680, 1937.

7. Hahn, P. F.; Bale, W. F.; Hetting, R. A.; Kamen, M. D., and Whipple, G. H.: Radioactive Iron and Its Excretion in Urine, Bile and Feces, J. Exper. Med. **70**:443, 1939.

8. Howard, R. B.; Balfour, W. M., and Cullen, R.: Extreme Hyperferremia in 2 Instances of Hemochromatosis with Notes on the Treatment of 1 Patient by Means of Repeated Venesections, J. Lab. & Clin. Med. **43**:848, 1954.

9. Balfour, W. M.; Hahn, P. F.; Bale, W. F.; Pommerenke, W. T., and Whipple, C. H.: Radioiron Absorption in Clinical Condition: Normal, Pregnancy, Anemia and Hemochromatosis, J. Exper. Med. **76**:15, 1942.

10. Davis, W. D., Jr., and Arrowsmith, W. R.: The Effect of Repeated Phlebotomies in Hemochromatosis, J. Lab. & Clin. Med. **39**:526, 1952.

¶ References 19-22.
# References 12 and 23.
* References 24 and 25.
† References 26-29.
‡ References 26, 27, and 29-31.
§ References 32 and 33.

11. Davis, W. D., Jr., and Laurens, H., Jr.: Correlation of Results of Liver Function Tests and Liver Biopsy in Hepatic Disease, South. M. J. **43:** 217, 1950.

12. Finch, C. A.; Hegsted, M.; Kinney, T. D.; Thomas, E. D.; Rath, C. E.; Haskins, D.; Finch, S., and Fluharty, R. G.: Iron Metabolism and the Pathophysiology of Iron Storage, Blood **5:**983, 1950.

13. Beyers, M. R., and Gitlow, S. E.: Metabolism of Iron in Hemochromatosis, Am. J. Clin. Path. **21:**349, 1951.

14. Davis, W. D., Jr., and Arrowsmith, W. R.: The Treatment of Hemochromatosis by Massive Venesection, Ann. Int. Med. **39:**723, 1953.

15. Houston, J. C.: Phlebotomy for Haemochromatosis: Effect of Removing 52 Pints of Blood in 16 Months, Lancet **1:**766, 1953.

16. Blackburn, C. R. B.; McGuinness, A. E., and Kaldor, I.: Removal of Excess Body Iron in Haemochromatosis by Repeated Venesection, Australasian Ann. Med. **2:**202, 1953.

17. Warthin, T. A.; Peterson, E. W., and Barr, J. H., Jr.: The Treatment of Idiopathic Hemochromatosis by Repeated Phlebotomy, Ann. Int. Med. **38:**1066, 1953.

18. Fineberg, S. K.: Diagnosis and Treatment of Hemochromatosis, New York J. Med. **54:**1915, 1954.

19. Rous, P., and Oliver, J.: Experimental Hemochromatosis, J. Exper. Med. **28:**629, 1918.

20. Cappell, D. F.: The Late Results of Intravenous Injection of Colloidal Iron, J. Path. & Bact. **33:**173, 1930.

21. Polson, C.: The Failure of Prolonged Administration of Iron to Cause Haemochromatosis, Brit. J. Exper. Path. **14:**73, 1933.

22. Menkin, V.: Experimental Hemosiderosis, Proc. Soc. Exper. Biol. & Med. **31:**755, 1934.

23. Taylor, J.; Stevin, D., and Reid, E. W.: Experimnetal and Idiopathic Siderosis in Cats, J. Path. & Bact. **41:**397, 1935.

24. Gillman, J.; Mandelstam, J., and Gillman, T.: A Comparison of Chemical and Histological Estimations of the Iron and Copper Content of the Livers of Africans in Relation to the Pathogenesis of Cytosiderosis and Cirrhosis (Haemochromatosis), South African J. M. Sc. **10:**109, 1945.

25. Gillman, J., and Gillman, T.: The Pathogenesis of Cytosiderosis (Haemochromatosis) as Evidenced in Malnourished Africans, Gastroenterology **8:**19, 1947.

26. Schwartz, S. O., and Blumenthal, S. A.: Exogenous Hemochromatosis Resulting from Blood Transfusions, Blood **3:**617, 1948.

27. Muirhead, E. E.; Cross, G.; Jones, F., and Hill, J. M.: Iron Overload (Hemosiderosis) Aggravated by Blood Transfusions, Arch. Int. Med. **83:**477, 1949.

28. Hemosiderosis and the Parenteral Administration of Iron, editorial, Ann. Int. Med. **36:**694, 1952.

29. Kleckner, M. S., Jr.; Baggenstoss, A. H., and Weir, J. F.: Hemochromatosis and Transfusional Hemosiderosis: A Clinical and Pathologic Study, Am. J. Med. **16:**382, 1954.

30. Chesner, C.: Hemochromatosis, J. Lab. & Clin. Med. **31:**1029, 1946.

31. Wyatt, J. P.; Mighton, H. K., and Moragues, V.: Transfusional Siderosis, Am. J. Clin. Path. **26:** 883, 1950.

32. Bomford, R. R., and Rhoads, C. P.: Refractory Anemia: I. Clinical and Pathological Aspects, Quart. J. Med. **10:**175, 1941.

33. Zeltmacher, K., and Bevans, M.: Aplastic Anemia and Its Association with Hemochromatosis, Arch. Int. Med. **75:**395, 1945.

Correspondence

BISHYDROXYCOUMARIN (DICUMAROL) THERAPY IN MYOCARDIAL INFARCTION

To the Editor:—The September, 1954, issue of the A. M. A. Archives of Internal Medicine includes a paper by Feldman and others on the controversial subject of Dicumarol [bishydroxycoumarin] therapy in moycardial infarction. May I take the liberty of pointing out an error of omission in the text which I believe results in an "editorialized" presentation of the data.

The concluding summary of the paper very properly quotes the number of thromboembolic complications in the control versus the treated group but makes no references to the mortality figures in each group. Likewise, the text quotes a total mortality of 15.6% but gives no figure for the mortality in the control versus treated groups other than to state that "There was no significant difference in the mortality rate." However, on examination of the detailed tables, which are broken down in several ways, one discovers that the mortality in the treated group is 10.0% while the mortality in the untreated group is 21.3%. While I do not doubt that each paired group in Tables 4 and 5 is too small to show statistically significant differences in mortality, I certainly feel that this lack of significance does not in any way support the implied contention that Dicumarol does not favorably influence the mortality rate. If the authors saw fit to conclude "There were seven thromboembolic complications in the group not receiving bishydroxycoumarin (Dicumarol) and six in the group under therapy with the anticoagulant" they should also have stated in the conclusions that there were 15 deaths in the treated group and 32 deaths in the untreated group.

I believe that each author has the privilege of interpreting his data according to his own dictates; however, I do not believe that an author should make a statement of "no significant difference" and refer only to a total mortality of 15.6% without any reference to the fact that his data shows 10.0% for the control group and 21.3% for the experimental. Granting that the group may be small for definite statistical conclusions, the mortality figures compare very favorably with those of Wright and others, who conclude the anticoagulants have an unquestionable effect on over-all mortality following myocardial infarction.

Murray Weiner, M.D.

To the Editor:—I wish to thank you for forwarding a copy of Dr. Murray Weiner's letter, in which he points to an "error of omission" in our article of Dicumarol [bishydroxycoumarin] therapy in myocardial infarction, that appeared in the September, 1954, issue of the A. M. A. Archives of Internal Medicine.

He points to the fact that, while we properly dwelled upon the lack of difference in the number of thromboembolic complications between the control and the treated group, no mention was made of the mortality figures in each group, being 10% in the treated group and 21.3% in the untreated.

This is neither an error of omission, thus detracting from the value of Dicumarol, nor of commission, to conceal an unknown but possibly beneficial effect of the drug besides that of lowering the prothrombic time. We realized that there was some difference in the mortality rate between the two groups, but we did not mention it. Hence, Dr. Weiner's quotation from our article is out of context. "There was no significant difference in the mortality rate" carries the impression that we were comparing the two groups. But the complete quotation dispels this, for it continues to read "or incidence of thromboembolic phenomena in the patients with or without hypertension, previous myocardial infarction history of previous angina, or the coexistence of diabetes mellitus." Therefore, it was the influence of associated conditions on the mortality rate or complications in the entire series that was compared and analyzed.

We made no reference to the difference in mortality for the following reasons. Firstly, the thromboembolic phenomena in the two groups were about the same. We feel that the controversial subject of anticoagulant therapy in myocardial infarction hinges mainly upon the difference in frequency of thromboembolism between the treated and the untreated. Secondly, as Dr. Weiner himself ultimately says about the figures in the various tables, the group is too small to show statistically significant differences in mortality, and thirdly, to interpret this insignificant difference in mortality in favor of Dicumarol, as Dr. Weiner so strongly suggests, is not warranted at present. For to subscribe to the contention held by some that anticoagulant drugs, even if they do not lower the incidence of thromboembolic phenomena, somehow influence favorably the over-all mortality rate in moycardial infarction, would tend to becloud the controversial subject of anticoagulants more than it already is. Therefore, let us adhere to the scientific fact, that the known action of the anticoagulant drug is to lower the incidence of thromoembolic complications in some patients. While we think it is not necessary to use it routinely, certain cases of myocardial infarction who are prone to develop such complications frequently benefit from anticoagulant therapy, and they should receive it.

L. FELDMAN, M.D.
8 South Michigan Ave.,
Chicago (3).

News and Comment

ANNOUNCEMENTS

Federal Grants for Medical Research.—Dr. Leonard A. Scheele, Surgeon General of the Public Health Service, U. S. Department of Health, Education, and Welfare, has announced approval of Federal grants for 972 medical research projects, totaling $10,275,533, for basic and applied research in many of the major diseases afflicting Americans today. The grants approved during recent meetings of the seven National Advisory Councils were scheduled for payment as of Dec. 1, 1954.

Two hundred eighty-nine of the awards, totaling $3,079,840, were for new research projects, and 683, totaling $7,195,693, were for continuation of existing projects.

The awards were made to scientists in approximately 215 research institutions in the United States and are administered by the National Institutes of Health, research bureau of the Public Health Service.

A tabulation of the grants follows:

	No. of Grants		Amount
National Institute of Arthritis and Metabolic Diseases	33	(New)	$ 275,155
	74	(Cont.)	723,548
National Institute of Neurological Diseases and Blindness	29	(New)	347,969
	55	(Cont.)	541,891
National Cancer Institute	79	(New)	799,916
	200	(Cont.)	2,764,914
National Institute of Dental Research	8	(New)	68,998
	3	(Cont.)	15,076
National Microbiological Institute	9	(New)	80,744
	33	(Cont.)	279,995
National Heart Institute	89	(New)	1,036,221
	169	(Cont.)	1,505,755
National Institute of Mental Health	15	(New)	204,664
	54	(Cont.)	577,979
Division of Research Grants	27	(New)	266,173
(for categories of medical and public health research not within the scope of the 7 Institutes)	95	(Cont.)	786,535
Totals	972		$10,275,533

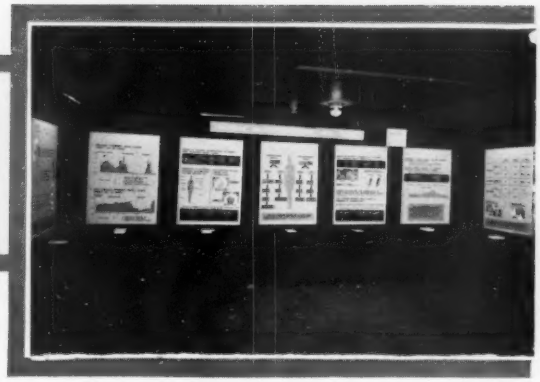
These amounts represent approximately 30% of the fiscal year 1955 funds (totaling $33,918,000) appropriated by Congress for medical research projects supported in whole or in part by Public Health Service grants.

The grants award program covers support of research in the medical and biological sciences, particularly the type of research dealing with causes and treatment of heart disease, cancer, mental illness, arthritis and the metabolic diseases (such as gout, liver diseases, diabetes), the neurological and sensory disorders (glaucoma, retrolental fibroplasia, multiple sclerosis, cerebral palsy, epilepsy), diseases of the teeth and mouth, and certain diseases of microbiological and parasitic origin (such as influenza, infectious hepatitis, the common cold, malaria, and schistosomiasis).

Other projects supported by P. H. S. research grants are concerned with fundamental exploration of metabolic and biological phenomena underlying the causes of most of the prevailing noninfectious diseases.

A full or partial listing of the individual grants, broken down by investigator, project title, amount of support, and research institution, is available from the Scientific Reports Branch, National Institutes of Health, Bethesda 14, Md., Telephone: OLiver 6-4000, Ext. 847.

Scientific Exhibits



ENDOCRINE THERAPY OF METASTATIC BREAST CANCER

OLOF H. PEARSON, M.D.
CHARLES D. WEST, M.D.
MIN CHIU LI, M.D
JOHN P. MACLEAN, M.D.
AND
NORMAN TREVES, M.D.
NEW YORK

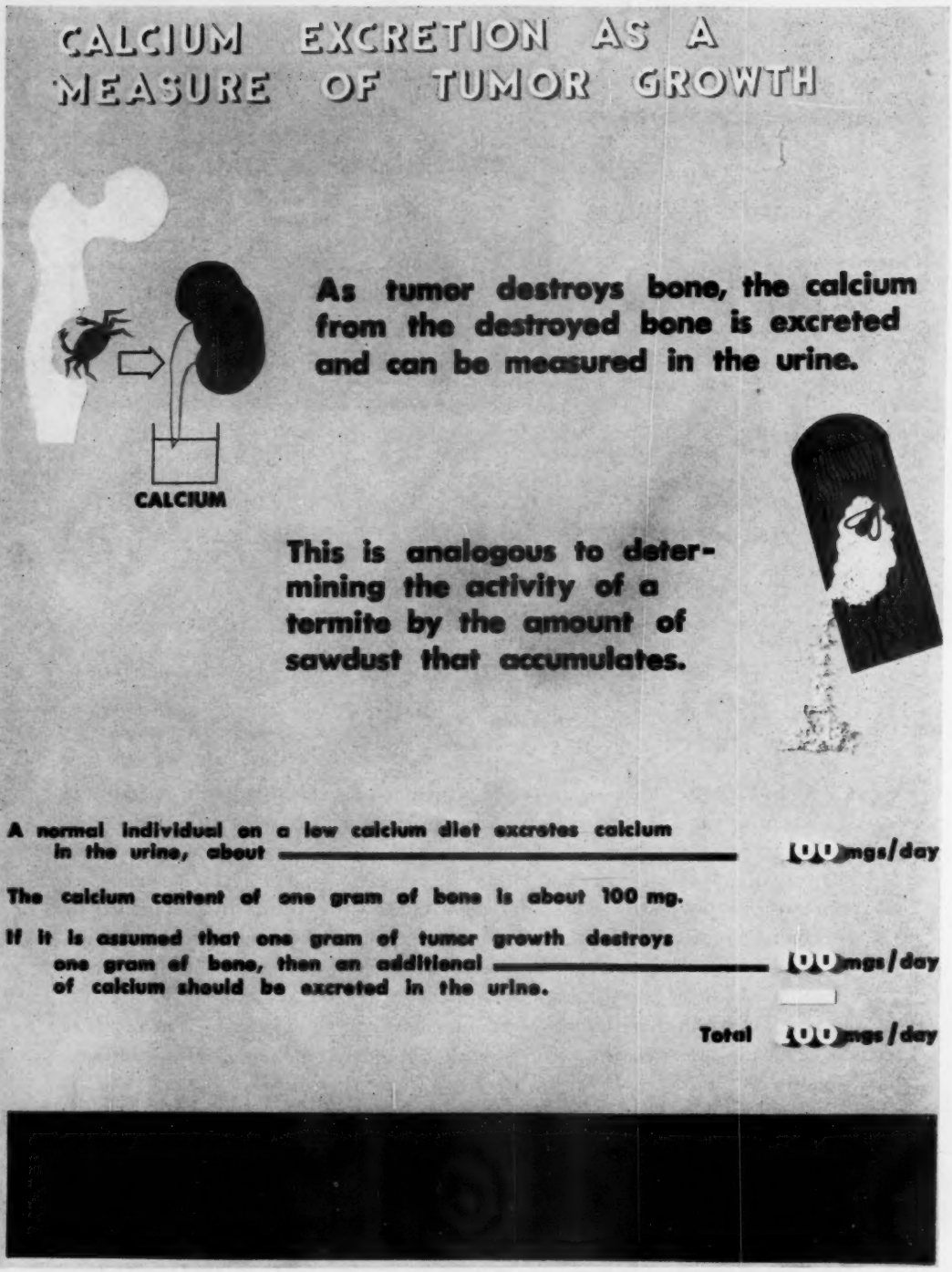
VARIOUS alterations of endocrine environment which result in therapeutic benefit in patients with metastatic mammary cancer are illustrated. The use of calcium excretion as a practical means of evaluating tumor growth in bone is shown. The results of surgical castration, bilateral adrenalectomy, and hypophysectomy are presented. A physiological basis for these methods of treatment is presented by demonstrating that certain hormones of the ovary, adrenal, and pituitary glands are important in maintaining the growth of mammary cancer. The therapeutic effects of cortisone, estrogens, and androgens are illustrated, with emphasis on the situations in which these hormones are most likely to be of benefit. The sequence of therapeutic measures which is most likely to produce optimum benefit is outlined.

From the Division of Clinical Investigation, Sloan-Kettering Institute for Cancer Research, and the Medical and Breast Services, Memorial and James Ewing Hospitals.

Shown as a scientific exhibit of the Section on Experimental Medicine and Therapeutics at the 103rd Annual Meeting of the American Medical Association, San Francisco, June 21-25, 1954.

These studies were supported in part by grants from the National Cancer Institute, National Institutes of Health, United States Public Health Service, C-925(C$_6$), C-2126; the United States Atomic Energy Commission; the American Cancer Society, Inc., and the Damon Runyon Memorial Fund.

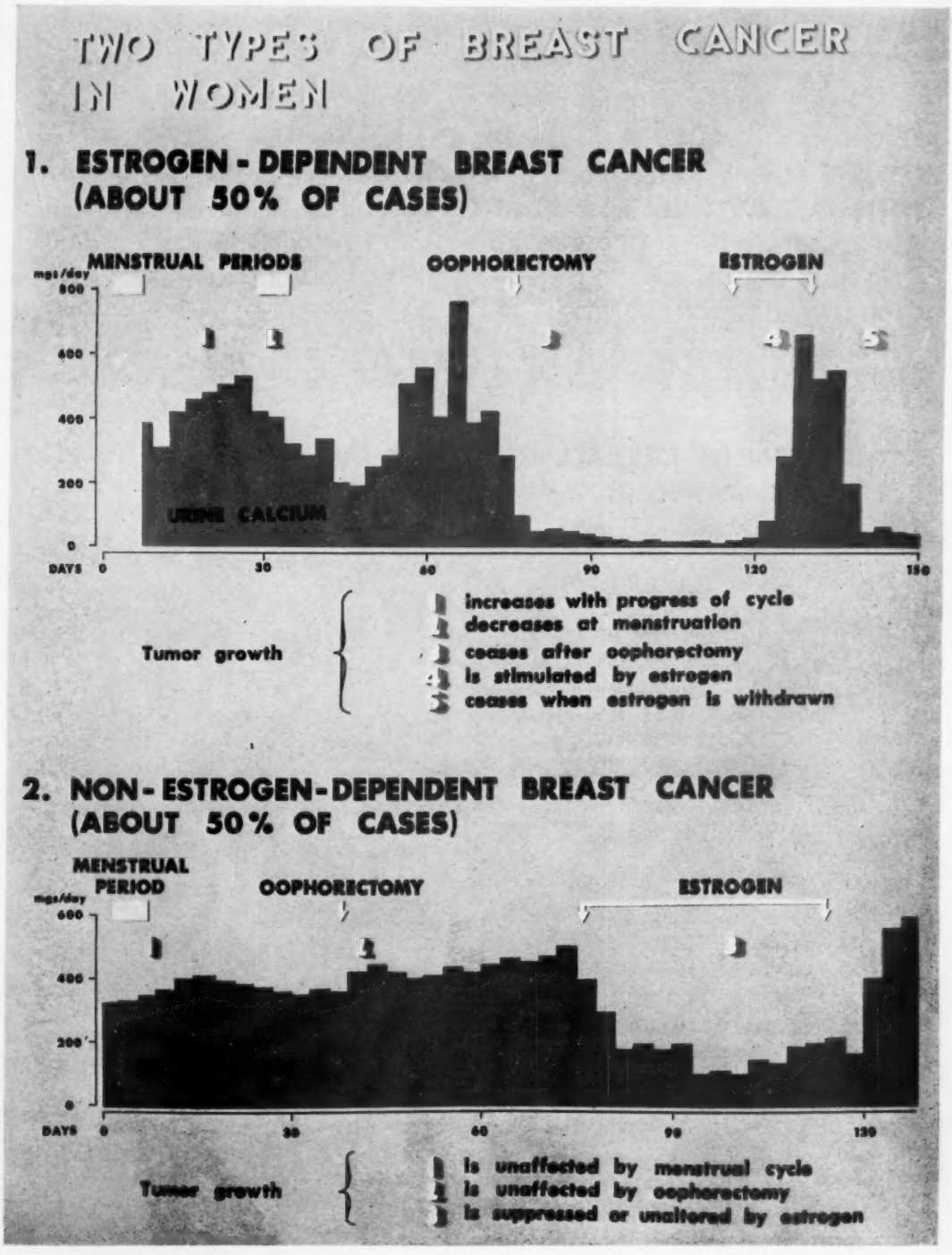
The authors wish to acknowledge the collaboration of Drs. Henry T. Randall, Bronson S. Ray, Willet F. Whitmore, Jr., Charles C. Harrold, Frank E. Adair, George C. Escher, James Green, John Finkbeiner, Joseph Farrow, Guy Robbins, Alfred A. Fracchia, Charles Breed Jr., Dorothy Sved, Richard Kaufman, and Jerome A. Urban.


CALCIUM EXCRETION AS A MEASURE OF TUMOR GROWTH
CALCIUM
As tumor destroys bone, the calcium from the destroyed bone is excreted and can be measured in the urine.
This is analogous to determining the activity of a termite by the amount of sawdust that accumulates.
A normal individual on a low calcium diet excretes calcium in the urine, about
100 mgs/day
The calcium content of one gram of bone is about 100 mg.
If it is assumed that one gram of tumor growth destroys one gram of bone, then an additional
100 mgs/day
of calcium should be excreted in the urine.
Total
100 mgs/day

REFERENCES

Pearson, O. H.; West, C. D.; Hollander, V. P., and Escher, G. C.: Alterations in Calcium Metabolism in Patients with Osteolytic Tumors, J. Clin. Endocrinol. **12**:926 (July) 1952.

Pearson, O. H., and West, C. D.: Objective Methods for the Measurement of Tumor Growth in Man, Proc. Am. A. Cancer Res. **1**:42 (April) 1953.



Pearson, O. H.; Hollander, V. P.; West, C. D.; Whitmore, W. F., Jr., and Randall, H. T.: Physiological Effects of Bilateral Adrenalectomy in Man, J. Clin. Invest. **31**:653 (June) 1952.

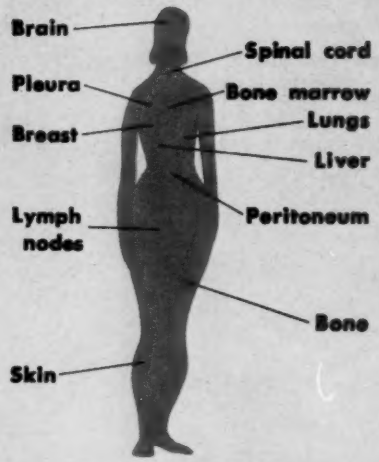
West, C. D.; Hollander, V. P.; Whitmore, W. F., Jr.; Randall, H. T., and Pearson, O. H.: The Effect of Bilateral Adrenalectomy on Neoplastic Disease in Man, Cancer **5**:1009-1018 (Sept.) 1952.

REMISSIONS INDUCED BY OOPHORECTOMY

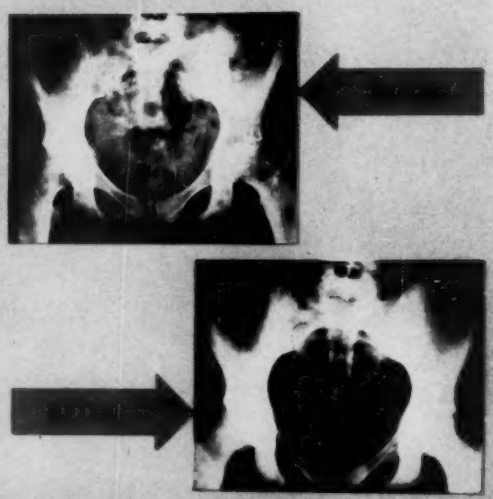
RESULTS OF BILATERAL OOPHORECTOMY IN WOMEN WITH METASTATIC BREAST CANCER

	Number of cases	Objective remissions	Duration of remission	
			Median	Average
Premenopausal	75	44%	6.5 mo.	9 mo.
Postmenopausal	21	10%	-	-

REGRESSION OF METASTASES FOLLOWING OOPHORECTOMY HAS BEEN OBSERVED IN:



RECALCIFICATION OF BONE LESIONS AFTER OOPHORECTOMY

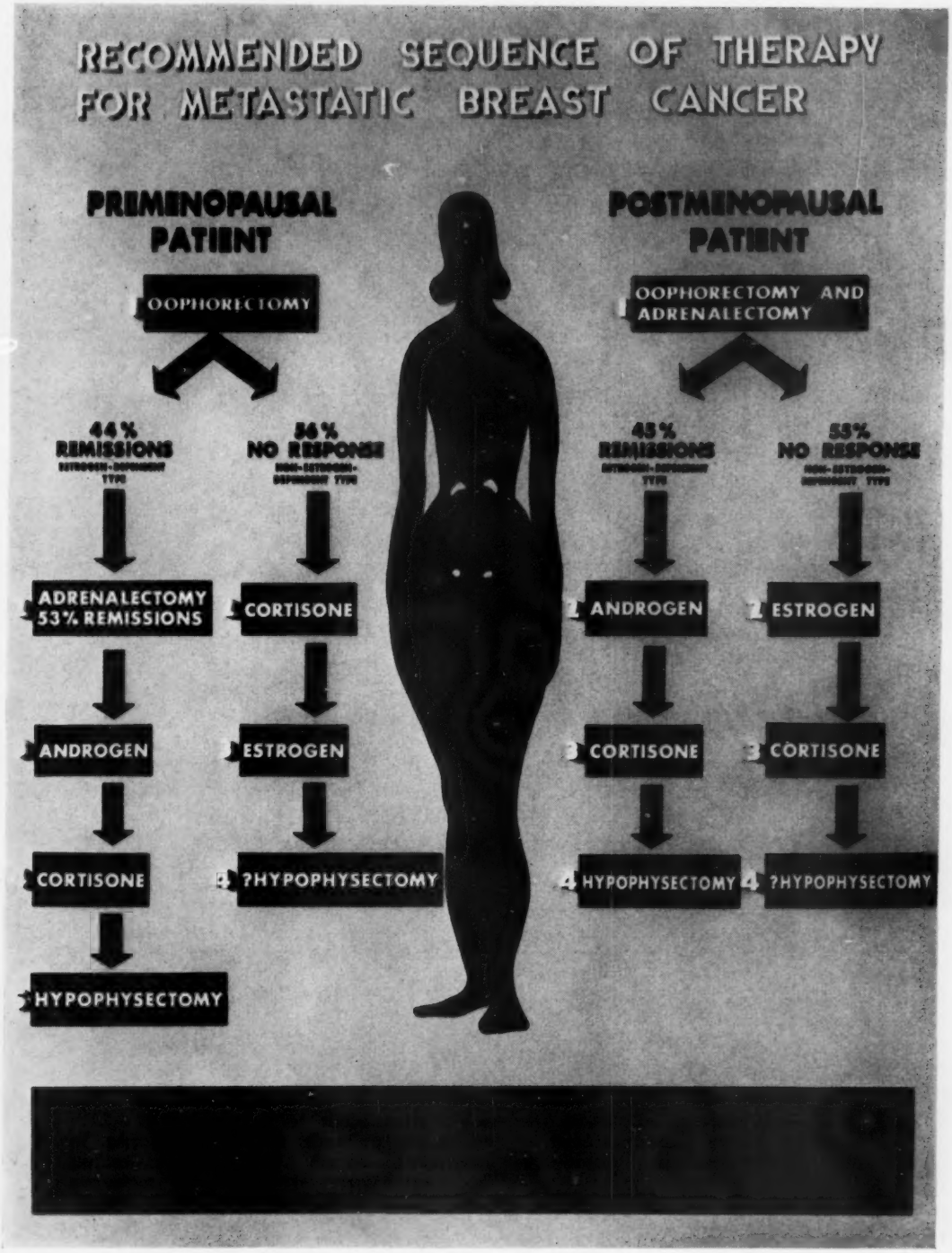


Neither the histologic picture of the cancer nor any clinical manifestations of the disease has been helpful in predicting a favorable response.

Huggins' histological type	Number responding to oophorectomy	Number not responding to oophorectomy
A	5	6
B	0	1
C	7	4
D	3	5

Hollander, V. P.; West, C. D.; Whitmore, W. F., Jr.; Randall, H. T., and Pearson, O. H.: Physiological Effects of Bilateral Adrenalectomy in Man, Cancer **5**:1019-1024 (Sept.) 1952.

Pearson, O. H.; Mendelsohn, M., and West, C. D.: Water and Salt Metabolism During Acute Adrenal Insufficiency in Man, J. Clin. Endocrinol. **13**:841 (July) 1953.



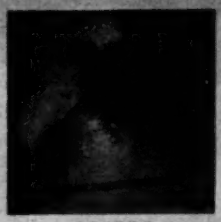
Pearson, O. H.; Whitmore, W. F., Jr.; West, C. D.; Farrow, J. H., and Randall, H. T.: Clinical and Metabolic Studies of Bilateral Adrenalectomy for Advanced Cancer in Man, Surgery **34**:543-556 (Sept.) 1953.

Randall, H. T.: An Evaluation of Adrenalectomy in Man: Physiological Changes and the Effect on Advanced Neoplastic Disease, Bull. New York Acad. Med. **30**:278 (April) 1954.

REMISSIONS INDUCED BY BILATERAL ADRENALECTOMY

RESULTS OF BILATERAL ADRENALECTOMY IN WOMEN WITH METASTATIC BREAST CANCER (all oophorectomized previously)

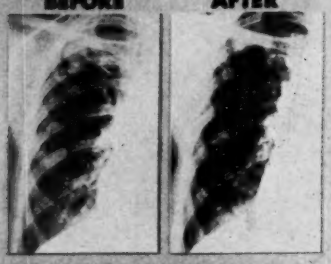
Number of cases	Objective remissions	Average duration of remissions	Average age
38	45%	> 7 mo.	45



BEFORE AFTER

REGRESSION OF RECURRENT CARCINOMA AFTER ADRENALECTOMY

REGRESSION OF PULMONARY METASTASES AFTER ADRENALECTOMY



BEFORE AFTER

COMBINED OOPHORECTOMY AND ADRENALECTOMY IN OLDER WOMEN (50-60) WITH METASTATIC BREAST CANCER

Produces objective remissions about as frequently as adrenalectomy does in the younger age group.

ONLY ESTROGEN-DEPENDENT BREAST CANCER IS SUPPRESSED BY ADRENALECTOMY

Of 17 patients who responded to oophorectomy ---------- 9 responded to adrenalectomy
Of 7 patients who failed to respond to oophorectomy ----- 0 responded to adrenalectomy

The histologic picture of the cancer is not a reliable index for predicting the response to adrenalectomy in our experience.

Huggins' histological type	Number responding to adrenalectomy	Number not responding to adrenalectomy
A	3	7
B	1	0
C	6	6
D	1	7

Pearson, O. H.; West, C. D., and Treves, N.: The Role of Ovarian Function in the Growth of Mammary Carcinoma in Man, J. Clin. Invest. **32**:594 (June) 1953.

Pearson, O. H.; Ray, B.; West, C. D.; Harrold, C. C.; Maclean, J. P., and Li, M. C.: Pituitary Somatotropin as a Growth Factor for Human Mammary Carcinoma, J. Clin. Invest. **33**:956-957, June 1954.

REMISSIONS INDUCED BY HYPOPHYSECTOMY

REGRESSION OF BREAST CANCER HAS BEEN OBSERVED FOLLOWING HYPOPHYSECTOMY

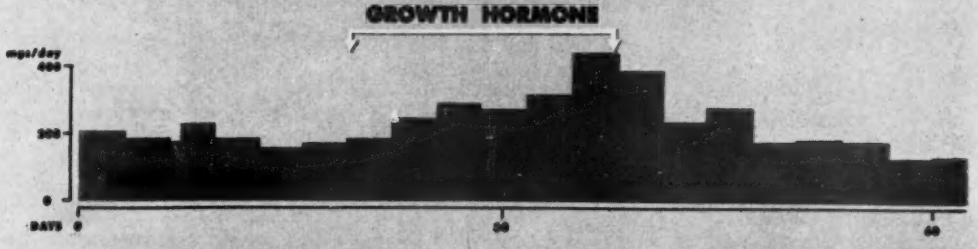
Does hypophysectomy induce remissions only by suppressing gonadal and adrenal function or are pituitary hormones also growth-promoting factors for breast cancer ?

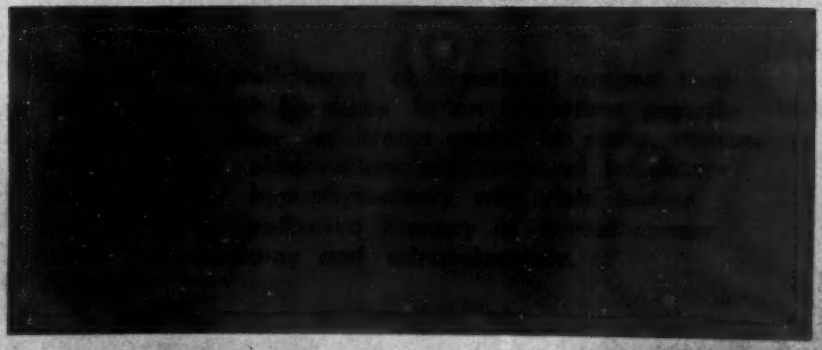
PITUITARY GROWTH HORMONE AS A GROWTH-PROMOTING FACTOR FOR BREAST CANCER

1 Results of hypophysectomy in 4 women who had previously obtained transient relief from oophorectomy and adrenalectomy

Objective remissions	Duration of remissions
50% (2 pts.)	> 9 months
	4 months

2 Acceleration of osteolytic metastases by pituitary growth hormone





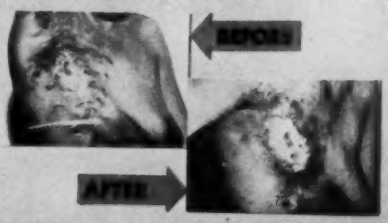
Pearson, O. H.; Ray, B.; Harrold, C. C.; West, C. D.; Li, M. C., and Maclean, J. P.: Effect of Hypophysectomy on Neoplastic Disease in Man, J. Clin. Endocrinol. **14**:828 (July) 1954.

West, C. D.; Li, M. C.; Maclean, J. P.; Rall, J. E., and Pearson, O. H.: Physiological Effects of Hypophysectomy in Man, J. Clin. Endocrinol. **14**:786 (July) 1954.

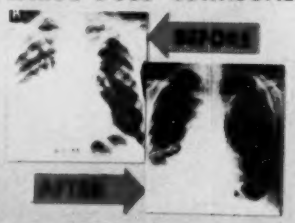
REMISSIONS INDUCED BY ANDROGEN, ESTROGEN AND CORTISONE

		Number of cases	Objective remissions	Duration mean	Duration median
ANDROGEN	Premenopausal (TESTOSTERONE PROPIONATE-100 mg 3 x / week)	54	13%	10 mo.	4 mo.
	Postmenopausal (SAME THERAPY)	113	20%	8 mo.	8 mo.
ESTROGEN	Postmenopausal (STILBESTEROL-15 mgs/day OR ETHINYL ESTRADIOL-3 mgs/day)	76	32%	13.5 mo.	8 mo.
CORTISONE	All ages 200-400 mgs/day	39	31%	3 mo.	-
	All ages 50-75 mgs/day	14	14%	-	-

REMISSION FROM SMALL DOSE CORTISONE



REMISSION FROM LARGE DOSE CORTISONE



Further observations are needed to determine whether remissions comparable to those obtained by adrenalectomy can be induced by cortisone, so-called "medical adrenalectomy."

West, C. D.; Li, M. C.; Maclean, J. P.; Escher, G. C., and Pearson, O. H.: Cortisone-Induced Remissions in Women with Metastatic Mammary Cancer, Proc. Am. A. Cancer Res. **1**:51-52 (April) 1954.

Pearson, O. H.; West, C. D.; Hollander, V. P., and Treves, N.: Evaluation of Endocrine Therapy for Advanced Breast Cancer, J. A. M. A. **154**:234-239 (Jan. 16) 1954.

METAMUCIL® IN CONSTIPATION

Normal Colon

Ulcerative Colitis

Atonic Colon

Smoothage in Correction of Colon Stasis

To initiate the normal defecation reflex, the "smoothage" and bulk of Metamucil provide the needed gentle rectal distention.

Once the habit of constipation has been established, due to any of a large number of causes, it becomes a major problem. Self-medication with irritant or chemical laxatives, or repeated enemas, usually causes a decreased, sluggish defecation reflex and may result in its complete loss.

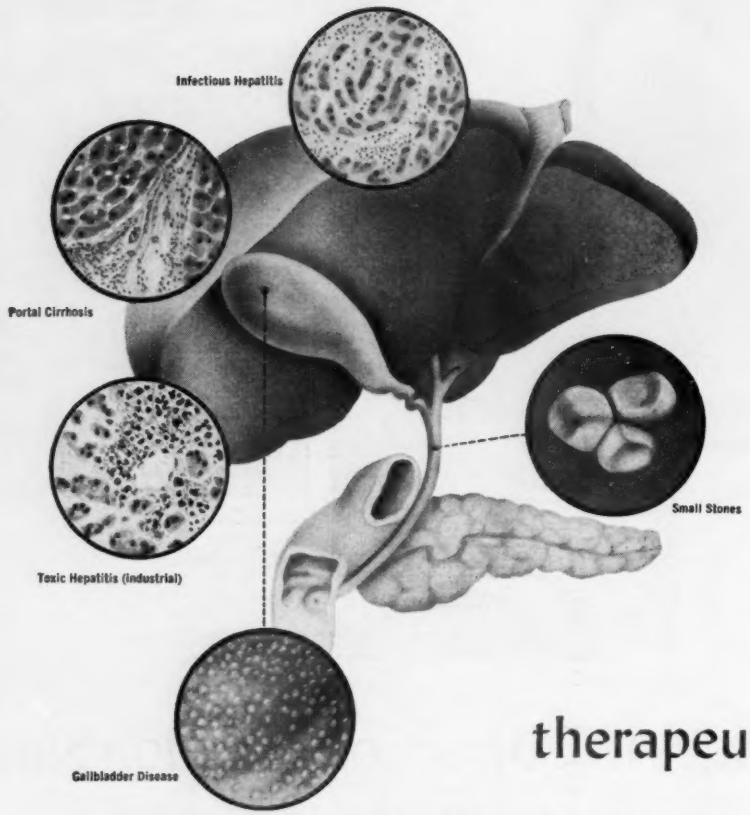
Rectal distention is a vital factor in initiating the normal defecation reflex, and sufficient bulk is thus of obvious importance in restoring this reflex. Metamucil provides this bulk in the form of a smooth, nonirritating, soft, hydrophilic colloid which gently distends the rectum and initiates the desire to evacuate. Metamucil demands extra fluid, imparting even greater smoothage to the intestinal contents.

It is indicated in chronic constipation of various types—including distal colon stasis of the "irritable colon" syndrome, the atonic colon following abdominal operations, repressions of defecation after anorectal surgery and in special conditions such as the management of a permanent ileostomy. Metamucil is the highly refined mucilloid of Plantago ovata (50%), a seed of the psyllium group, combined with dextrose (50%) as a dispersing agent.

The average adult dose is one rounded teaspoonful of Metamucil powder in a glass of cool water, milk or fruit juice, followed by an additional glass of fluid if indicated.

Metamucil is supplied in containers of 4, 8 and 16 ounces. It is accepted by the Council on Pharmacy and Chemistry of the American Medical Association. G. D. Searle & Co., Research in the Service of Medicine.

SEARLE



therapeutic bile

in liver and gallbladder disorders

"...due to the production of true hydrocholeresis–
a marked increase both in volume and fluidity of the bile."*

"...the objectives of the principal therapy cannot but be furthered...."*

"...confirmed further by the clinical experiences reported."*

DECHOLIN® and DECHOLIN SODIUM®

(dehydrocholic acid, *Ames*) (sodium dehydrocholate, *Ames*)

Decholin Tablets, 3¾ gr. (0.25 Gm.); bottles of 100, 500, 1000. *Decholin Sodium*, 20% aqueous solution; ampuls of 3 cc., 5 cc. and 10 cc.; boxes of 3, 20 and 100.

*Schwimmer, D.; Boyd, L. J., and Rubin, S. H.: Bull. New York M. Coll. *16*:102, 1953.

AMES COMPANY, INC · ELKHART, INDIANA

Ames Company of Canada, Ltd., Toronto

63155

Enriched Bread

a Valiant Guardian Against Deficiency Disease

As a result of the nationwide enrichment of bread, the average American consumes notably more thiamine, riboflavin, niacin, and iron.[1] Enriched bread has thus served as a vigilant guardian against beriberi, ariboflavinosis, pellagra, and iron-deficiency disease.[2]

According to calculated values, the food supply of the nation during 1942-1948 provided 25 per cent more thiamine, 10 per cent more riboflavin, 15 per cent more niacin, and 14 per cent more iron than it would have without the nationwide enrichment of bread and flour.[3,4]

In consequence of this nutritional enhancement of the nation's food supply, enriched bread has been a material aid in improving national nutritional health.[2,4,5,6]

Enriched bread also supplies important amounts of high-grade protein, calcium, and nutrient energy. Its protein, comprising flour protein and milk protein, contributes significantly to sound growth and tissue maintenance.

1. Groggins, P.H.: The High Price of Eating Well, J. Agr. & Food Chem. *1*:1124 (Nov. 25) 1953.
2. Sebrell, W.H., Jr.: Trends and Needs in Nutrition, J.A.M.A. *152*:42 (May 2) 1953.
3. Nutrients Available for Consumption per Capita per Day, 1909-1948, United States Department of Agriculture, Miscellaneous Publication 694, 1949.
4. Jolliffe, N.: The Pathogenesis of Deficiency Disease, in Jolliffe, N.; Tisdall, F.F., and Cannon, P.R.: Clinical Nutrition, New York, Paul B. Hoeber, Inc., 1951, Chap. 1.
5. Flour and Bread Enrichment, 1949-50, The Committee on Cereals, Food and Nutrition Board, National Research Council, 1950.
6. Sherman, H.C.: The Nutritional Improvement of Life, New York, Columbia University Press, 1950, pp. 86-87.

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

AMERICAN BAKERS ASSOCIATION

20 NORTH WACKER DRIVE • CHICAGO 6, ILLINOIS

In Myocardial Infarction

C·R·P·A*

C-Reactive-Protein Antiserum — Schieffelin

A highly sensitive test for presence of inflammation

- Investigators have found this test to be consistently negative in cases of cardiac insufficiency uncomplicated by myocardial infarction and inflammation.[1,4]
- based upon presence of specific C-reactive protein in serum of patients with certain inflammatory diseases — characteristic precipitin reaction develops upon addition of C·R·P·A to serum of such patients . . . C-reactive protein is never found in normal serum.[2]
- simple, economical, routine laboratory procedure that has been demonstrated to be the most consistently positive test in the presence of rheumatic activity[3] . . . often reveals presence of subclinical inflammatory reactions . . . detects relapse or recurrence of inflammatory disease . . . and aids in gauging adequacy of therapeutic regimens.
- "False positive tests do not occur since CRP is not present, even in trace amounts, in normal sera"[3] . . . accurate qualitative reading may be made within 30 minutes . . . preliminary quantitative estimate obtained within 2 hours.

For detailed instructions on the materials and techniques required for the use of C·R·P·A — Schieffelin, just send us a request and we will mail you a descriptive brochure.

1. Kroop, I. G. and Shackman, N. H.: Proc. Soc. Exper. Biol. & Med. 86:95 (May) 1954.
2. Wood, H. F., and McCarty, M.: J. Clin. Investigation 30:616 (June) 1951.
3. Stollerman, G. H., et al.: Am. J. Med. 15:645 (Nov.) 1953.
4. Hedlund, P.: Acta med. Scandinav., Supplement 196:579, 1947.

Supplied: 1 cc. vials (30-40 determinations)

Schieffelin & Co., Pharmaceutical and Research Laboratories since 1794

18 Cooper Square, New York 3, N. Y.

*trademark